TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects

Compound Number: GSK1265744

Development Phase: IIB

Effective Date: 16-NOV-2017

Protocol Amendment Number: 07

Authors: PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N168152_00	2013-JUL-12	Original
2013N168152_01	2013-OCT-08	Amendment No.:01
Updated protocol summary, clarified study drug naming conventions, updated T&E tables, clarified study drug descriptions, clarified IDMC, clarified health outcomes timings and questionnaires, additional miscellaneous changes		
2013N168152_01	2013-OCT-11	Amendment No.:01
Republished for administrative formatting change, however, incorrect signature page used.		
2013N168152_02	2013-OCT-16	Amendment No.:01
Republished for corrected signature page.		
2013N168152_03	2013-OCT-28	Amendment No.:01
Republished to clarify revision chronology; corrected Section 6.3 treatment administration		
2013N168152_04	2014-JAN-23	Amendment No.: 02
Primary modifications: Study design adapted to consolidate the Induction Period into a single 20 Week arm and for the addition of an every 8 week IM regimen into the Maintenance Period. Increased sample size to 265 subjects. Primary endpoint changed from Week 24 to Week 32. Dose rationale updated.		
2013N168152_05	2014-JUN-13	Amendment No.: 03:
Primary modifications: Epzicom / Kivexa added as Investigational Product beginning at Day 1 of the Maintenance Period; clarification that alternative background therapy (if positive for HLA-B*5701) is not counted as the protocol permitted switch for NRTI; clarification regarding provision of alternative NRTI therapy; change in visit window for subjects on the oral dosing arm; excursion temperatures added for Epzicom / Kivexa and Edurant; text added for Epzicom / Kivexa overdose; deleted option for subject informed consent by legal representative; Time and Events Table clarifications. Additional clarifications and typographical corrections throughout.		
2013N168152_06	2015-APR-22	Amendment No. 4
Primary modifications: Addition of a 2-hour post dose pharmacokinetic samples and ECG at Week 32 and Week 48 for subjects receiving intramuscular GSK744 LA and		

TMC278 LA. Addition of LAI116482 Week 96 data. Addition of maladministration of injection risk. Additional clarifications for injection site reaction collection. Clarified visit windows.		
2013N168152_07	2016-JUN-21	Amendment No. 5
Primary modifications: Allowed subjects to remain on their randomized IM regimens during the extension period (rather than switching to a single selected IM regimen as originally planned). Allowed subjects randomized to the oral arm to switch to one of the optimized Q8W/Q4W regimens (using proposed phase 3 dosing schedules, see Section 5.1.6), based on subject preference. Added Dose Rationale for optimized IM dosing based off new modelling. New exploratory objectives and endpoints added for evaluation of maintenance and optimized Q8W/Q4W regimens at Week 128 and 152. Updated study design schematic for extension phase. Dosage and Administration Table updated to include details on optimized IM regimens. Time and Events tables updated to reflect updated Extension Period IM dosing schedule. Added Extension Period PK assessments for subjects switching to the optimized IM regimens. Added new study 'Extension Switch Population' for the 'Week 128 analysis'. Added IDMC monitoring of number of PDVFs for subjects switching from oral treatment to optimized IM regimens. Added Week 128 Extension Switch Analysis and a Week 152 Analysis		
2013N168152_08	2017-AUG-14	Amendment No. 6 (United States Specific Amendment)
This United States specific amendment has been developed to assess the amount of peak drug concentrations (both cabotegravir [CAB] and rilpivirine [RPV] long acting injectables [LAI]) that enters the Central Nervous System and more specifically, the cerebrospinal fluid (CSF) after subjects receive an injection of the LAI CAB and RPV in the LATTE-2 study. This amendment will also characterize the plasma concentration of CAB/RPV LAI obtained at the same time point as the CSF analysis and will also assess the relationship between the peak concentration of CAB/RPV in the CSF with the amount of HIVRNA in the CSF using a sensitive HIVRNA assay called single copy assay		
2013N168152_09	2017-NOV-16	Amendment No. 7
This amendment is to update a planned interim analysis from Week 152 to Week 160.		

SPONSOR SIGNATORY

PPD

PPD Kimberly Smit PPD
VP Global Me
ViiV Healthcar

11/16/2017
Date

PPD

SPONSOR INFORMATION PAGE

Clinical Study Identifier: 200056

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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Regulatory Agency Identifying Number(s):

US IND 109,678

EudraCT # 2013-000783-29

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200056

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

τ	Dosing interval, time between consecutive doses
3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC(0-τ)	Area under the plasma drug concentration-time curve from predose to the end of the dosing interval at steady state
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood urea nitrogen
Cτ	Concentration at the end of a dosing interval
c/mL	Copies/millilitre
CAB	Cabotegravir, Oral
CAB LA	Cabotegravir, Long Acting Injectable
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
Cmax	Maximum plasma drug concentration
CPK	Creatine Phosphokinase
CV	Coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	Electrocardiograph
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
FC	Fold Change
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTC	Emtricitibine
GCP	Good Clinical Practices
GI	Gastrointestinal
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HbsAg	Hepatitis B Virus surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High Density Polyethylene
HIV-1	Human Immunodeficiency Virus Type 1
HIVMQ	HIV medication questionnaire
HIVTSQ	HIV treatment satisfaction questionnaire
HIVTSQc	HIV Treatment Satisfaction Questionnaire change version

HIVTSQs	HIV Treatment Satisfaction Questionnaire status version
HSR	Hypersensitivity reactions
IAS	International AIDS Society
IB	Investigator's Brochure
IC90	90% Inhibitory Concentration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IM	Intramuscular
INI	Integrase Inhibitor
INR	International Normalized Ratio
IP	Investigational Product, both formulations of cabotegravir and rilpivirine
IRB	Institutional Review Board
ISR	Injection Site Reaction
ITT	Intent-to-Treat
ITT-ME	Intent-to-Treat Maintenance Exposed
IUD	Intrauterine Device
IV	Intravenous
LA	Long acting
LLOD	Lower limit of detection
LSLV	Last Subject Last Visit
mg	Milligram
mL	Milliliter
MSDF	Missing, Switch or Discontinuation = Failure
MSDS	Material Safety Data Sheet
ng	Nanogram
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case
PD	Pharmacodynamic
PDVF	Protocol Defined Virologic Failure
PGx	Pharmacogenetics
PI	Protease Inhibitor
PK	Pharmacokinetic
Pol	Polymerase
PopPK	Population Pharmacokinetics
PP	Per Protocol population
PRO	Patient Reported Outcomes
PSRAE	Possible Sucidiality Related Adverse Event
PT	Prothrombin Time
Q4W	Every 4 Weeks
Q8W	Every 8 Weeks
QT_C	Corrected QT interval
RAP	Reporting analysis plan
RBC	Red blood cell
RNA	Ribonucleic acid

RPV	Rilpivirine, Edurant, oral formulation of TMC278
RPV LA	Rilpivirine, Long Acting Injectable
RT	Reverse transcriptase
SAE	Serious adverse event
SPM	Study Procedure Manual
SVF	Suspected Virologic Failure
t1/2	Estimated terminal phase half-life
TDF	Tenofovir disoproxyl fumarate, Viread
TLOVR	Time to Loss of Virologic Response
ULN	Upper limit of normal
US	United States
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cells
WD	Withdrawal

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PROTOCOL SUMMARY

Study Terms

For the ease of the reader, the following terms will be useful to understand:

- Cabotegravir (GSK1265744) – the ViiV compound under study. When written as shown, this refers to either the oral or long acting formulation.
    - CAB – the oral formulation of cabotegravir;
    - CAB LA – the long acting injectable formulation of cabotegravir; LA stands for "long acting";
- Rilpivirine – the Janssen / partner compound under study. When written as shown, this refers to either the oral or long acting formulation.
    - RPV – rilpivirine or the oral formulation of rilpivirine, also known as Edurant;
    - RPV LA - the long acting injectable formulation of rilpivirine; LA stands for "long acting";
- Induction – the induction of virologic suppression of Human Immunodeficiency Virus Type 1 (HIV-1) infection in anti-retroviral naive subjects prior to the initiation of the CAB LA + RPV LA regimen. This period will be represented in text, schema and Time and Events as negative weeks. The length of induction is 20 weeks. Baseline is the first day of the Induction Period (i.e. this is not Day 1).
- Maintenance – the maintenance of virologic suppression of HIV-1 infection; the length of maintenance being evaluated is 96 weeks. Day 1 is the first day of the Maintenance Period.
- Dosing Regimen - Two intramuscular (IM) dosing regimens are being evaluated: every 4 weeks (Q4W) and every 8 weeks (Q8W). One oral dosing is being evaluated (oral).
- Extension – extending study treatment past the key study analysis points; length of extension being evaluated is until investigational product (IP) is either locally approved and commercially available, a subject no longer derives clinical benefit, a subject meets a protocol-defined reason for discontinuation or until development of IP is terminated.
- Long-Term Follow-Up – follow up period for subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued treatment or have been withdrawn; length of follow up being evaluated is 52 weeks.

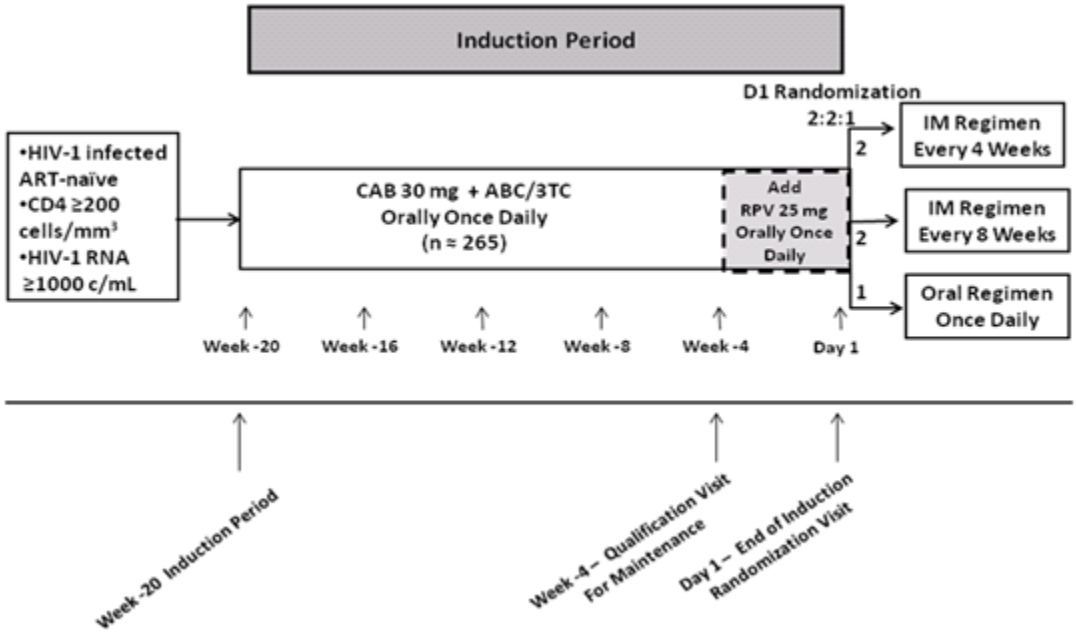
- IP = Investigational product; both formulations of CAB and RPV. Epizcom / Kivexa (ABC/3TC) will also be considered IP beginning at Day 1 of the Maintenance Period.

Study Objective

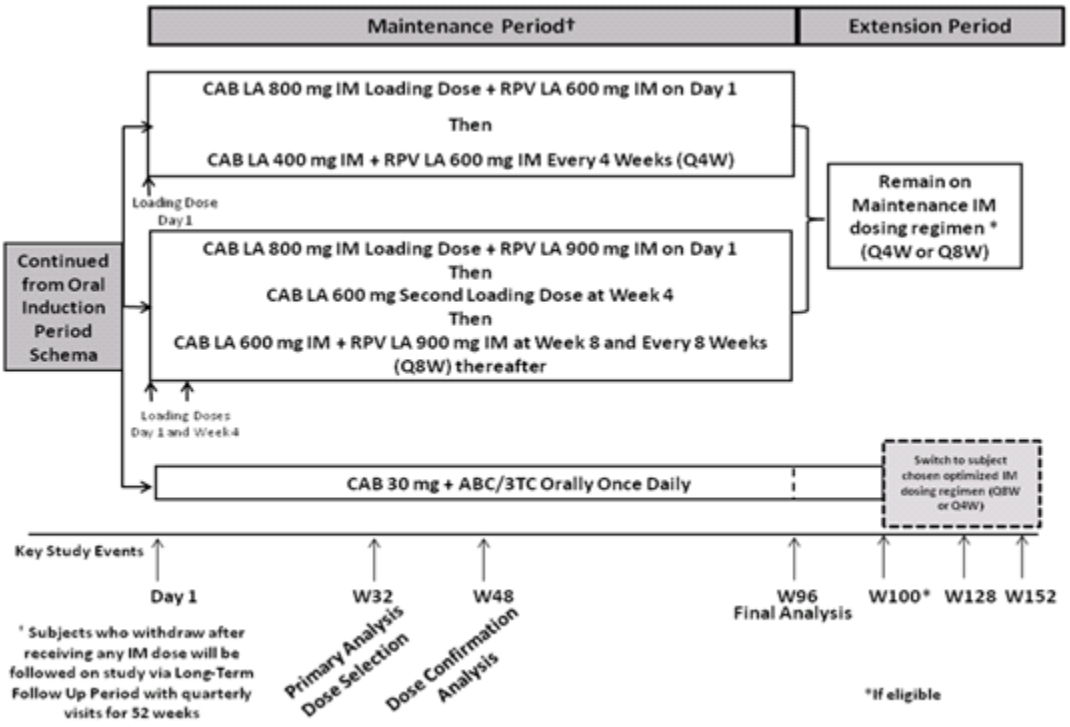
The overall objective of this study is to select an intramuscular dosing regimen of CAB LA plus RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of the two IM dosing regimens, relative to CAB 30 mg plus abacavir (ABC)/lamivudine (3TC) orally once daily.

Study Schematic

Induction Period



Maintenance and Extension Period



Notable Inclusion Criteria

- Male or female subjects at least 18 years old that are HIV-1 positive (HIV-1 ribonucleic acid (RNA) ≥1000 copies/millilitre [c/mL])
- Women of childbearing potential may be enrolled if they agree to use adequate contraception for the life of the study and at least 52 weeks after withdrawal from an IM regimen.
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate).
- Antiretroviral therapy (ART) naive (no more than 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection. Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor will be exclusionary).

Notable Exclusion Criteria

- Any evidence of primary resistance based on the presence of any major resistance-associated mutation (International AIDS Society [IAS]-USA, 2013) in the Screening result or, if known, any historical resistance test result.
- Subjects with known moderate to severe hepatic impairment.

- History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (Hepatitis B Virus Surface Antigen [HBsAg] positive). Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy must be excluded.
- History of liver cirrhosis with or without hepatitis viral co-infection.
- Current or anticipated need for chronic anti-coagulation.
- Any verified Grade 4 laboratory abnormality.
- Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound.
- Subject has estimated creatinine clearance <50 mL/min via Cockcroft-Gault method.
- Alanine aminotransferase (ALT) ≥5 times upper limit of normal (ULN). Subjects with ALT > 2xULN but <5xULN may participate in the study, if in the opinion of the Investigator and GlaxoSmithKline (GSK) medical monitor the lab abnormality will not interfere with the study procedures or compromise subject safety.
- ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
- Subjects who are HLA-B*5701 positive and unable to use an alternative nucleoside reverse transcriptase inhibitor (NRTI) backbone (subjects who are HLA-B*5701positive may be enrolled if they use an alternative NRTI backbone that does not contain abacavir).
- Any clinically significant finding on screening or Baseline electrocardiograph (ECG).
- Tattoo or other dermatologic condition over gluteus region.
- Need for chronic anticoagulants.

Study Design

Study 200056 is a Phase IIb, randomized, multicentre, parallel group, open-label, three-part study to be conducted in approximately 265 HIV-1 infected ART-naive adults. This study will consist of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn IM dosing regimen subjects only).

Induction Period

Following the 28-day Screening Period, eligible subjects will be enrolled into the study and begin a 20-week Induction Period utilizing an oral regimen of CAB 30 mg once daily plus ABC/3TC 600/300 mg once daily.

Subjects will initiate treatment on their first day on study and will be seen every 4 weeks for study treatment dispensing and safety and efficacy assessments.

At Week (-4) the treatment regimen is modified to add RPV 25 mg once daily for the remainder of the Induction Period.

Eligibility for the Maintenance Period

Subjects who have demonstrated tolerability to the Induction Period regimen and with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week (-4) are not eligible to enter the Maintenance Period, will not be allowed a repeat to determine eligibility and will therefore be withdrawn from the study.

Maintenance Period

At Day 1, the Maintenance Period begins. Eligible subjects will be randomized 2:2:1 to receive an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 96 weeks, an IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks for 96 weeks, or to continue on the oral Induction Period regimen of CAB 30 mg + ABC/3TC once daily for 96 weeks (or 100 weeks if continuing on to the Extension Period). Subject randomization will be stratified by subjects' HIV-1 RNA prior to Week (-8) (<50 c/mL, yes or no).

On the first day of the Maintenance Period (Day 1), subjects will receive their last dose of the Induction regimen (CAB 30 mg+ABC/3TC+RPV 25 mg) in the clinic and initiate either IM injections or be dispensed the oral regimen depending on the randomization arm. Add-on RPV treatment will be discontinued for all subjects after Day 1.

Dosing for each arm is as follows (all injections are single injections per drug unless otherwise noted):

IM injections every 8 weeks (Q8W)

- Day 1 only – CAB LA 800 mg (loading dose delivered as two 400 mg IM injections) + RPV LA 900 mg IM
- Week 4 only - CAB LA 600 mg IM (second loading dose, no RPV LA)
- Week 8 - CAB LA 600 mg IM + RPV LA 900 mg IM every 8 weeks for 96 weeks

IM injections every 4 weeks (Q4W)

- Day 1 only - CAB LA 800 mg (loading dose delivered as two 400 mg IM injections) + RPV LA 600 mg IM
- Week 4 - CAB LA 400 mg IM + RPV LA 600 mg IM every 4 weeks for 96 weeks

Oral Control Arm

- CAB 30 mg + ABC/3TC once daily for 96 weeks (or 100 weeks if going on to the Extension period)

It is important to note that keeping to the subject's dosing / visit schedule is a very important component to the study. IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). A (+ or -) 7-day window, from the projected visit date, is allowable for IM dosing but not preferred. At one-week post dose visits (Week 1, Week 25, and Week 41), there is no defined visit window, rather visits should occur approximately 1 week from the last injection.

Visits for subjects on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3-day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit. Visits in Long Term Follow Up are to occur as projected from the last injection with a (+ or -) 3-day visit window, from the projected visit date.

All subjects are seen approximately every 4 weeks for safety, efficacy and PK assessments through Week 32. After Week 32, subjects will continue to be seen as per the Time and Events Schedule (see Section 6) for dosing, safety, efficacy and PK assessments through Week 96 (or Week 100 for the oral arm if continuing on to the Extension Period).

Some visits that are not aligned with dosing will be conducted by telephone interview. This allows for safety assessments to be conducted at all visits, but limits clinic visits for non-dosing visits.

See the Time and Events Schedule Section 6.2 and Section 6.3 for more information. See Section 3.2.5.3 for additional information regarding special requirements from Week 96 to Week 104 for subjects on the oral arm entering the Extension Period.

Eligibility for the Extension Period

Subjects who have demonstrated tolerability to their Maintenance Period regimen and with an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit are eligible to enter the Extension Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week 96 are not eligible to enter the Extension Period, will not be allowed a repeat to determine eligibility and will therefore be withdrawn from the study.

Extension Period

Both IM dosing regimen (Q8W and Q4W) will continue to be evaluated in the Extension period.

Entering from the CAB LA + RPV LA Arms

All subjects who successfully complete 96 weeks of CAB LA + RPV LA treatment in the Maintenance Period as described in Section 3.2.5.1, will continue with their current IM dosing regimen of CAB LA and RPV LA in the Extension Period until:

- study treatment is locally approved and commercially available,
- the subject no longer derives clinical benefit,
- the subject meets a protocol-defined reason for discontinuation
- until development of either CAB LA or RPV LA is terminated.

Subjects will remain on their current regimen after Week 96 and will continue to receive their Maintenance Period IM dosing regimen for the remainder of study participation. Safety and efficacy assessments will be conducted every 16 weeks. Dosing visits will occur according to the selected dosing regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.

Entering from the CAB 30 mg + ABC/3TC Arm

All subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option to continue study participation by switching to an optimized IM dosing regimen of their choice (either Q8W or Q4W) of CAB LA + RPV LA in the Extension Period. Subjects not choosing to switch to an optimized long acting regimen will complete their study participation at Week 96.

Subjects who choose to continue on to the Extension Period will be assessed for eligibility to begin their selected CAB LA + RPV LA regimen. Subjects will continue on their Maintenance regimen (CAB 30 mg + ABC/3TC) while eligibility is being confirmed. RPV will not be added to their Maintenance regimen prior to the switch to optimized IM dosing. Subjects were given RPV during the last 4 weeks of the Induction Period to evaluate safety and tolerability before being randomized to continue in the Maintenance Period and thus further evaluation is not necessary.

Participants with a Week 96 HIV-1 RNA <50 c/mL, will continue their oral regimen (CAB 30 mg + ABC/3TC) until Week 100. In order to qualify to receive CAB LA + RPV LA injections at Week 100, the HIV-1 RNA results from the Week 96 visit must be undetectable (<50 c/mL; a single repeat HIV-1 RNA test may be allowed prior to Week 100 following consultation with the Medical Monitor).

If the Optimized Q4W IM Dosing Regimen is Selected by the Subject

At visit Week 100, participants will return to the clinic, take the last dose of their oral regimen (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104 and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104, but not later than Week 104, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 injection, the interval between injection visits

should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds, or is projected to exceed, 5 weeks.

If the Optimized Q8W IM Dosing Regimen is Selected by the Subject

At visit Week 100, subjects will return to the clinic, take the last dose of their oral (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second loading injections will be administered at Week 104 (CAB LA 600 mg + RPV LA 900 mg, with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 8 weeks thereafter. The dosing window for the second injection allows administration between Week 103 and Week 104, but preferably not later than Week 104. Starting at the Week 112 injection, the interval between injection visits should be limited to a maximum of 9 weeks. If the length of time between injections exceeds, or is projected to exceed 9 weeks, the Medical Monitor must be contacted to discuss individual subject case management. After Week 112, a dosing window (±7 days) for injections is allowed, but not preferred.

Subjects will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

Safety and efficacy assessments will be conducted as per the Time and Events Schedule (See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.)

Subjects not eligible to enter the Extension Period will end their study participation and will complete the Withdrawal Visit. Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

Long-term Follow-Up Period IM Regimens

Any subject who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive Highly Active Antiretroviral Treatment (HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. This period is considered study participation and subjects will be followed on study during this time.

In the Long-Term Follow-Up Period, subjects will receive oral HAART and be followed for 52 weeks after the last dose of CAB LA and/or RPV LA. In order to assure that subjects have access to HAART during the Long-Term Follow-Up Period, GSK may supply HAART regionally or reimbursement will be provided during this period.

Follow Up Visit

A Follow up visit may be conducted approximately 4 weeks after the last dose of IP and is required only if the subject has ongoing adverse events (AEs) or lab abnormalities at the last on-study visit.

Key Study Assessments

- HIV-1 RNA and CD4+ cell counts
- Laboratory assessments including hematology, blood chemistry, urinalysis and fasting glucose, lipids and pregnancy testing
- PK assessments including 2-hour post dose samples at Day 1, Weeks 32, 48, 100 and 128.
- Monitoring and recording of all AEs and serious adverse events (SAEs)
- Physical exams and vitals
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history)
- HIV-associated conditions
- Exercise habits utilizing a subject diary
- Electrocardiograms
- Assessment of Injection Site Reactions (ISRs) clinically and utilizing a subject diary
- Columbia Suicide Severity Rating Scale (eC-SSRS)
- Health Outcomes questionnaires for treatment satisfaction and medication adherence

Definition of Virologic Failure

- Non-response as indicated by a less than a 1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA after 4 weeks of starting the Induction Period, which is subsequently confirmed, unless the plasma HIV-1 RNA is < 400 c/mL.
- Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥ 200 c/mL after prior suppression to < 200 c/mL.

- Rebound as indicated by two consecutive plasma HIV-1 RNA that are > 0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the lowest HIV-1 RNA value is ≥ 200 c/mL.

Permitted Treatment Substitutions

Subjects who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on an approved dual-NRTI backbone that does not contain abacavir (e.g. tenofovir/emtricitibine [TDF/FTC]). This regimen may be supplied regionally by GSK or reimbursement will be provided.

Switch of background NRTI therapy to an alternative approved NRTI therapy for toxicity or tolerability management is allowed once during the study. Switches of a background NRTI for any other reason are not permitted in the study.

In exceptional circumstances, the medical monitor may authorize the use of CAB and/or RPV (oral regimen) as a short-term "bridging" strategy for subjects who have begun CAB LA + RPV LA. This strategy would only be employed to address any potential gap in CAB LA + RPV LA dosing as a result of scheduling conflicts which would prevent planned dosing.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will evaluate the efficacy, tolerability, and safety of CAB and RPV before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. This IDMC review may be conducted after approximately 45 subjects have reached Week 8 of the Maintenance Period, depending on IDMC agreement. In addition, futility guidance is included to monitor the performance of all treatment arms when 50% of subjects have completed Week 24 of the Maintenance Period in order to prevent subjects from continuing on a dosing regimen if existing data indicates that subjects are at unacceptable risk of inadequate maintenance of virologic suppression.

As subjects enter the Maintenance Period of the study, if the number of protocol defined virologic failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. Similar thresholds will be used by the IDMC to monitor the number of protocol defined virologic failures for subjects switching from oral CAB 30 mg +ABC/3TC to an optimized IM dosing regimen during the Extension Period. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

If one of the IM dosing regimens (Q8W or Q4W) is discontinued as a result of an IDMC review or any subsequent analysis (as detailed in the IDMC Charter), those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued IM dosing regimen, or selected a discontinued optimized

IM dosing regimen, may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

Primary Analysis

The Week 32 primary analysis will be conducted once the last randomized subject has completed the Week 32 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of both IM dosing regimens of CAB LA + RPV LA and to select a regimen for further development.

1. INTRODUCTION

1.1. Background

It is estimated that 34 million people are currently living with HIV/ acquired immunodeficiency syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of 2.5 million new infections and cause 1.7 million deaths per year [UNAIDS, 2012]. While advances in the development of new antiretroviral therapies (ART) provide extensive insights into the management of HIV-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires that we continue to improve on the durability, tolerability and convenience of all antiretroviral classes. There is an enduring need to develop new agents with improved safety and resistance profiles and convenient dosing for both antiretroviral treatment-naïve and treatment-experienced patients.

1.2. List of Study Terms

For the ease of the reader, the following terms will be useful to understand:

- Cabotegravir (GSK1265744) – the ViiV compound under study. When written as shown, this refers to either the oral or long acting formulation.
    - CAB – the oral formulation of cabotegravir;
    - CAB LA – the long acting injectable formulation of cabotegravir; LA stands for “long acting”;
- Rilpivirine (TMC278) – the Janssen / partner compound under study. When written as shown, this refers to either the oral or long acting formulation.
    - RPV – rilpivirine or the oral formulation of rilpivirine, also known as Edurant;
    - RPV LA - the long acting injectable formulation of rilpivirine; LA stands for “long acting”;
- Induction – the induction of virologic suppression of Human Immunodeficiency Virus Type 1 (HIV-1) infection in anti-retroviral naive subjects prior to the initiation of the CAB LA + RPV LA regimen. This period will be represented in text, schema and Time and Events as negative weeks. The length of induction is 20 weeks. Baseline is the first day of the Induction Period (i.e. this is not Day 1).
- Maintenance – the maintenance of virologic suppression of HIV-1 infection; the length of maintenance being evaluated is 96 weeks. Day 1 is the first day of the Maintenance Period.

- Dosing Regimen - Two intramuscular (IM) dosing regimens are being evaluated: every 4 weeks (Q4W) and every 8 weeks (Q8W). One oral dosing is being evaluated (oral).
- Extension – extending study treatment past the key study analysis points; length of extension being evaluated is until investigational product (IP) is either locally approved and commercially available, a subject no longer derives clinical benefit, a subject meets a protocol-defined reason for discontinuation or until development of IP is terminated.
- Long-Term Follow-Up – follow up period for subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued treatment or have been withdrawn; length of follow up being evaluated is 52 weeks.
- IP = Investigational product; both formulations of CAB and RPV. Epzicom / Kivexa will also be considered IP beginning at Day 1 of the Maintenance Period.

1.3. Cabotegravir (GSK1265744) – Oral (CAB)

CAB is an integrase inhibitor with potent *in vitro* and *in vivo* inhibition of HIV-1. CAB shows low nanomolar activity against a broad range of HIV-1 strains, including clinical isolates with documented raltegravir resistance. Human pharmacokinetics (PK) data with the oral formulation support once daily dosing without the use of a pharmacokinetic enhancer. Potent short-term antiviral activity of once daily dosing of CAB was demonstrated during 10-day monotherapy in integrase-naïve HIV-1 infected subjects. Mean reductions from Baseline on Day 11 plasma HIV-1 ribonucleic acid (RNA) were 2.14 and 2.55 $\log_{10}$ copies/millilitre (c/mL) at the CAB doses of 5 mg and 30 mg once daily, respectively [GlaxoSmithKline Document Number RM2009/00485/00 and GlaxoSmithKline Document Number RM2008/00633/00].

Data from the non-clinical toxicology evaluations conducted to date with CAB have not identified any progression-limiting toxicity. CAB has been administered in early phase clinical studies at doses between 5-50 mg in single or repeat doses or for up to 10 days. Of 187 subjects participating across all Phase I and IIa oral studies, the most frequent adverse events (AEs) (>3 subjects) observed during CAB dosing were headache (13.9%), nausea (4.3%), and dizziness (3.8%) [Lou, 2013].

Through Phase I and Phase IIa studies conducted to date, there have been no CAB related Grade 2-4 AEs or serious serious adverse events (SAEs) reported. No CAB laboratory trends have been identified. An ongoing Phase IIb study of CAB, LAI116482 is described below (see Section 1.7).

1.4. Cabotegravir – Long Acting Injectable (CAB LA)

CAB LA, a long acting injectable formulation of cabotegravir, has been dosed in 136 healthy subjects. Subjects have received single or repeat doses of CAB LA at doses between 100 to 800 mg, either intramuscularly (IM) or subcutaneously (SC) and either alone or in combination with RPV LA (study LAI114433 [single dose LA, n=58], study

LAI115428 [repeat dose LA, n=40], and study LAI116815 [single dose LA, n=38]). The adverse event (AE) profile has been similar to those of CAB (oral). To date, no studies in HIV-1 infected subjects have been conducted with CAB LA.

CAB LA has been generally well-tolerated as either an IM or SC dose. Intramuscular injection site reactions (ISRs) have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date. Erythema, nodules, induration, and warmth at the injection site were most commonly reported in healthy subjects. Painless nodules were more common following SC injections than IM injections. No treatment emergent serious AEs have been reported in any of the healthy volunteer studies involving CAB LA. [LAI115428 GlaxoSmithKline Document Number 2011N112455_03 and GlaxoSmithKline Document Number RM2010/00170/04: LAI114433].

All of the above characteristics make cabotegraivir an attractive compound for continued HIV drug development.

1.5. Rilpivirine – Oral (RPV)

RPV, the oral formulation of rilpivirine (Edurant), is a diarylpyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with *in vitro* activity against wild type HIV-1 and select NNRTI-resistant mutants. RPV is currently approved as a 25 mg oral tablet formulation in multiple countries such as the United States (US), EU and Canada for use in antiretroviral (ARV) treatment-naïve patients as per the approved label in each country / region. Review and approval in other countries is ongoing. RPV combines once daily dosing with potent antiviral activity and a good tolerability/safety profile. The approval of RPV is based on Week 96 safety and efficacy analyses from 2 randomized, double blind, active controlled Phase III trials in ART treatment-naive subjects.

The Phase III trials (TMC278-C209 [Molina, 2011] and TMC278-C215 [Cohen, 2011]) compared RPV to efavirenz (EFV) each with a background regimen of 2 NRTIs, in antiretroviral-naïve HIV-1 infected subjects with HIV-1 RNA ≥ 5000 c/mL and no NNRTI resistance. Both trials were identical in design, with the exception of the background regimen. The Week 48 efficacy outcome for the pooled data from TMC278-C209 and TMC278-C215 (N=1368) showed that the proportion of subjects with HIV-1 RNA < 50 c/mL was 83% for RPV based regimen compared to 80% for the EFV based regimen (Snapshot algorithm). The overall virologic failure rate was 13% for the RPV compared to 9% for EFV. The proportion of patients who discontinued study due to an adverse event or death was 2% for RPV and 7% for EFV [Cohen, 2012].

1.6. Rilpivirine – Long Acting Injectable (RPV LA)

Rilpivirine is also formulated as a long acting injectable (RPV LA) with PK that could support IM dosing every 4 or 8 weeks. Results from 3 completed Phase I trials (TMC278-TiDP15-C146 [C146] and TMC278-TiDP15-C158 [C158]) have provided an understanding of the safety and tolerability after parenteral RPV LA dosing, as well as its pharmacokinetic characteristics. Seventy subjects have received RPV LA injectable

suspension in these trials. To date, no studies in HIV-1 infected subjects have been completed with RPV LA.

The results of study C146 demonstrated that RPV LA was generally well tolerated at all doses (200, 400, or 600 mg) and with all injection routes (IM and SC). Overall, there were no RPV LA signs of systemic intolerance. The incidence of ISRs was dependent on the type of administration and dose volume: better tolerability was observed for doses of 1 or 2 mL vs 3 mL in volume. No clinically relevant safety issues were identified with respect to laboratory parameters, vital signs, and electrocardiograph (ECGs).

In C158 (N=20), RPV LA injectable suspension in the current formulation after single IM injection of 300 mg or of 600 mg, or after multiple dosing regimens of 3 successive IM doses was generally safe and well tolerated. Successive monthly IM administration (1200, 600, and 600 mg) of RPV LA was also well tolerated with few AEs and ISRs. No deaths or SAEs related to the trial medication were reported. The most frequently reported AEs were headache (4 subjects [23.5%]) and mild injection site reactions (5 subjects [29.4%]). There were no clinically relevant effects on laboratory parameters, ECGs, and vital signs (TMC278 [Rilpivirine, oral and parenteral] Integrated Investigator's Brochure, 2013).

In LAI115428, RPV LA was administered as successive monthly IM injections as 1200/900 mg or 1200/600 mg along with CAB LA. As noted in Section 1.4, the injections were generally well tolerated, no subject discontinued due to an ISR, and no treatment emergent serious AEs were reported [GlaxoSmithKline Document Number 2011N112455_03].

1.7. Study LAI116482

LAI116482 is an ongoing Phase IIb dose-ranging study (CAB 10 mg, 30 mg, 60 mg) evaluating the utility of a two-drug, two-class combination (CAB + RPV) when both are given as a once daily oral regimen following induction of virologic suppression using CAB plus 2 investigator selected NRTIs. Eligible subjects enter Maintenance at Week 24 where they begin the CAB + RPV regimen.

To date, the study has enrolled 244 subjects, 181 of whom received one of three oral dose regimens of CAB (10 mg, 30 mg or 60 mg) plus 2 NRTIs. A planned Week 96 (24 weeks on Induction and 72 weeks on two-drug Maintenance) analysis is complete and demonstrated similar antiviral activity across the three dosing arms of CAB in combination with RPV, which compared favorably to the control regimen of EFV 600 mg once daily plus 2 NRTIs.

Rates of protocol defined virologic failure (PDVF) through Week 96 were low across all study arms. Three subjects receiving CAB (one at each dose) and three subjects receiving EFV were characterized as PDVFs during Induction. During Maintenance, three subjects receiving CAB (10 mg, n=2; and 30 mg, n=1) and two subjects receiving EFV were characterized as PDVF.

During Maintenance, treatment emergent integrase inhibitor (INI) (Q148R) and NNRTI (E138Q) resistance mutations were identified in one subject on CAB (10 mg). The subject experienced suspected virologic failure (SVF) at Week 48, which was subsequently confirmed. There was no change in RPV susceptibility, and a 3.08 fold change in susceptibility to CAB. The subject reported starting an extreme low calorie diet prior to SVF. Week 26 and Week 36 RPV pre-dose concentrations for the subject were lower than concentrations seen in the Phase III RPV studies. The subject also had lower CAB predose concentrations in Maintenance compared to Induction. The Week 40 and Week 48 PK for this subject was consistent with Maintenance Phase Individual Average pre-dose values determined prior to the reported dates of calorie restriction.

One subject on CAB (10 mg) developed treatment emergent NNRTI resistance (K101K/E and E138E/A). The subject experienced virologic failure at Week 72 which was subsequently confirmed. There was no change to CAB susceptibility, and a 4.6 fold change in susceptibility to RPV. There was no treatment-emergent integrase resistance.

By Week 16 or at time of IP discontinuation if before Week 16, 63% of subjects were treated with Truvada (tenofovir/emtricitibine, TDF/FTC) as their background dual NRTI and 37% of the subjects were treated with EPZICOM/KIVEXA™ (abacavir/lamivudine, ABC/3TC). Similar virologic response rates (HIV-1 RNA < 50 c/mL) through 24 weeks were seen in subjects taking CAB + ABC/3TC (87%) and in subjects taking CAB + TDF/FTC (86%).

Following induction therapy, CAB + RPV (86%) maintained virologic suppression at a rate similar to EFV + NRTIs (83%) through 96 weeks. There was a numerically lower response rate of CAB 10 mg and CAB 30 mg, relative to CAB 60 mg, but this was largely due to non-virologic discontinuations, with a low PDVF rate across all arms.

The most common treatment-emergent AEs reported for subjects on any of the CAB doses, were upper respiratory tract infections, diarrhea, nausea, and headache. One subject receiving CAB 60 mg and one subject receiving CAB 30 mg had a Grade 3 headache. The Grade 3 headache for the CAB 60 mg subject occurred very early, study day 3, while the Grade 3 headache for the CAB 30 mg subject occurred on study day 343. The majority of AEs were Grade 1 (29%) or Grade 2 (49%) severity. Seven subjects on CAB versus nine on EFV withdrew due to an AE, one receiving 10 mg (ECG abnormal and palpitations), two receiving 30 mg (panic attack, Burkitt's lymphoma) and four receiving 60 mg (hepatitis, transaminases increased, anxiety disorder and musculoskeletal pain). The majority of CAB related AEs were Grade 1 and few of those AEs led to withdrawal through Week 96 (n=4 [2%]). There have been no CAB drug related SAEs to date.

Two of the subjects that withdrew due to AE met liver stopping criteria with an alanine aminotransferase (ALT)>10x upper limit of normal (ULN) at approximately Week 4 and Week 8 after initiating study drug. Both had pre-existing steatohepatitis and were dosed with CAB 60 mg + ABC/3TC. Both subjects remained asymptomatic, had normal serum bilirubin levels and had resolution of the ALT values after drug discontinuation. These 2 subjects accounted for the only Grade 3-4 ALT abnormalities in this study to date. Overall, the rates of any graded ALT or aspartate aminotransferase (AST) abnormality

were similar between CAB and EFV dosed subjects through Week 96: ALT: 20% and 21% respectively; AST: 25% and 21% respectively.

These data from LAI116482 support the conduct of study 200056 by demonstrating the antiviral activity of CAB when used initially as part of a HAART regimen to induce virologic suppression. In addition, this data confirmed antiviral activity of CAB + RPV as a two-drug oral Maintenance regimen and provides proof of principle for CAB LA + RPV LA as a maintenance regimen.

Based upon the results through Week 96 of the LAI116482 study [Margolis, 2015], and in accordance with the pre-specified dose selection criteria at Week 48, a 30 mg oral dose of CAB has been selected to be used in combination with ABC/3TC for induction of virologic suppression in study 200056.

All ongoing subjects in the LAI116482 study have entered the Open Label Extension phase to continue to receive the two drug regimen of CAB 30 mg + RPV 25 mg. All subjects had completed 48 weeks of the Maintenance regimen by the time study 200056 began dosing any IM regimen, permitting a robust evaluation of the virologic efficacy of the oral two drug regimen of CAB and RPV, prior to initiating the long acting injectable regimen. These data will be made available to Investigators.

1.8. 200056

The 200056 study (LATTE-2) evaluated a 20 week induction of HIV-1 RNA suppression with a three drug oral antiretroviral regimen consisting of CAB + ABC / 3TC Fixed Dose Combination (FDC) followed by randomization to a two-drug regimen consisting of intramuscular (IM) long-acting (LA) CAB LA + RPV LA compared to continuation of oral CAB + ABC / 3TC for the maintenance of HIV-1 RNA suppression. A total of 309 participants were enrolled and treated.

During the Induction Period there was a rapid and sustained decline in HIV-1 RNA, with 91% of participants (282/309) achieving HIV-1 RNA <50 c/mL through 20 weeks of therapy. There was a single participant (with known compliance issues) with confirmed virologic failure during the Induction Period. Virologic testing revealed no treatment emergent phenotypic or genotypic resistance in this participant.

The primary endpoint for 200056 was the Week 32 proportion of participants with HIV-1 RNA < 50 c/mL (Snapshot, Intent-to-Treat Maintenance Exposed population [ITT-ME]). Following virologic suppression on three drug oral therapy in the Induction Period, 286 participants qualified to enter randomization at the Day 1 visit, and were subsequently randomized 2:2:1 onto every 4 week intramuscular (IM) injections with CAB LA + RPV LA (Q4W), every 8 week IM injections with CAB LA + RPV LA (Q8W) or continuation of oral CAB + NRTIs, respectively. At the time of randomization at Day 1, participants entering one of the IM arms discontinued all oral ART. Through 32 weeks of two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes, compared to 91% of participants continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms. Through 32 weeks of Maintenance therapy, there was one

participant each on Q8W and oral dosing with confirmed virologic failure (CVF), without any evolution of viral resistance. The CVF on Q8W dosing occurred following an aberrant RPV injection, without measurable plasma RPV concentrations 4 weeks post dosing.

Week 48 data was a secondary endpoint for 200056, and permitted the evaluation of the two-drug long-acting combinations' ability to maintain the virologic suppression demonstrated at Week 32. At Week 48, 92% (Q8W) and 91% (Q4W) of participants receiving injectable dosing had a sustained virologic response (HIV-1 RNA <50 c/mL) compared to 89% of participants continuing oral CAB + 2 NRTIs. Although the proportion of participants with virologic success was similar for Q8W and Q4W dosing, the reason for Snapshot failure was different between the arms. There were more Snapshot failures for virologic reasons on the Q8W arm (n=8, 7%) than in the Q4W arm (n=1, <1%), and more participants with no virologic data (discontinued due to AE or other reasons) on the Q4W arm (n=9, 8%) compared to the Q8W arm (n=1, <1%).

Between Week 32 and Week 48, one additional participant (Q8W) had confirmed virologic failure. This participant had a Baseline HIV-1 RNA of 444,489 c/mL. At Week 48, the participant was a suspected virologic failure with HIV-1 RNA = 463 c/mL. Upon retest, ten days later, the virologic failure was confirmed with HIV-1 RNA of 205 c/mL. At the time of CVF, this participant had treatment emergent NNRTI resistance K103N, E138G, and K238T, with high level phenotypic resistance to delaviridine (>MAX), efavirenz (48 fold change [FC]), nevirapine (>Max), and rilpivirine (3.34 FC). The fold change to etravirine (1.91) was below the lower cutoff. Week 48 integrase genotype had the treatment emergent integrase resistance mutation Q148R, with accompanying resistance to raltegravir (29 FC), elvitegravir (138 FC), and cabotegravir (6.06 FC). The Week 48 sample was not resistant to dolutegravir (1.38 FC).

Overall, AEs and clinical chemistries were similar to those observed in prior studies with CAB, without discernible trends between Q8W, Q4W, and oral. Injections were well tolerated with two participants discontinuing due to injection tolerability through 48 weeks (both on Q8W dosing). The vast majority of injection site reactions were due to pain/discomfort with nearly all injection site reactions classified as mild (82%) or moderate (17%), with <1% of reactions classified as severe. There was no discernible tolerability difference between Q4W (2 mL) dosing and Q8W (3 mL dosing). The most common non-ISR AEs during the Maintenance Phase were nasopharyngitis (24%), headache (16%), and diarrhea (13%) on IM arms and nasopharyngitis (30%), headache (11%), and diarrhea (5%) on oral CAB. Through Week 48, SAEs during the Maintenance Period occurred in 7% of participants randomized to CAB LA + RPV LA and 5% of participants randomized to remain on oral treatment, none were drug related. Based on the data from the Week 48 endpoint, Q4W dosing was chosen to progress for further clinical development in Phase 3 studies, however, due to continued interest in evaluating the potential of Q8W dosing, subjects entering the Extension Period from the oral CAB 30 mg + ABC/3TC arm in this study will be given the option to switch to either an optimized Q8W or Q4W regimen. Subjects originally randomized to the IM regimen and entering the extension phase will remain on their randomized regimen.

1.9. Study Rationale

While advances in the development of new anti-retroviral therapies (ART) provide extensive insights into the management of HIV-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with the long-term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. There is an enduring need to develop new agents with improved safety and resistance profiles with convenient dosing for both antiretroviral treatment-naive and treatment-experienced patients.

Various approaches to simplify a patient's antiretroviral therapy (ART) regimen, after achieving virologic suppression, have been studied. Previous studies have evaluated switches to ritonavir-boosted PI monotherapy therapy in virologically suppressed patients [Bierman, 2009 and Arribas, 2012]. While the data from these studies have shown both long-term non-inferiority and inferiority to continual Highly Active Antiretroviral Therapy (HAART), they suggest that simplifying from a three drug dual class regimen to a single boosted protease inhibitor may be a safe and effective option for the majority of subjects studied who have effectively maintained virologic suppression.

This clinical trial, 200056, will evaluate a different simplification approach (see Section 3.1 for study schematic). In this study, subjects will induce HIV-1 RNA suppression with a three drug antiretroviral regimen consisting of CAB + ABC/3TC FDC and then switch to a two-drug two-class regimen consisting of CAB LA + RPV LA for the maintenance of HIV-1 RNA suppression.

The overall objective of this study is to select an intramuscular dosing regimen of CAB LA plus RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg plus ABC/3TC orally once daily, in HIV-1 infected antiretroviral-naïve subjects.

This study consists of three parts: an Induction Period, Maintenance Period and Extension Period. There is also a Long-Term Follow Up Period for subjects who withdraw and have received at least one dose of CAB LA and / or RPV LA.

Induction Period

The objective of the Induction Period is to induce virologic suppression prior to the initiation of the CAB LA + RPV LA regimen. In addition, the Induction Period will evaluate the safety, tolerability and efficacy of CAB in combination with ABC/3TC in HIV-1-infected, ART-naive adults. The Induction Period consists of an evaluation of CAB 30 mg once daily plus ABC/3TC through 20 weeks. Virologic suppression in the LAI116482 study was rapid, with 83% of CAB 30 mg treated subjects achieving an HIV-1 RNA <50 c/mL by Week 8 suggesting that the majority of subjects in the 200056 study will be virologically suppressed for at least 12 weeks prior to randomization into the Maintenance Period. A review of the virology data from LAI116482 suggests that few subjects required greater than 16 weeks of therapy to achieve virologic suppression

(HIV-1 RNA <50 c/mL), including subjects who entered the study with HIV-1 RNA >100,000 c/mL.

Unless subjects meet a study withdrawal criterion, their regimen will be modified during Induction at Week (-4) by adding on RPV 25 mg orally once daily. RPV is being added to the ART regimen for all subjects at Week (-4) to establish safety and tolerability of RPV in individual subjects prior to initiating treatment with CAB LA + RPV LA during the Maintenance Period. Subjects who do not or cannot tolerate CAB or RPV during this period should not enter the Maintenance Period. At the majority of time points, the incidence of (treatment related) AEs in the Phase III RPV studies were comparable between the RPV and control group and highest during the first 4 weeks of treatment. Median time to onset of first rash events was 10.5 days. No grade 4 rash events were reported. In addition, this RPV add on will serve as a pharmacokinetic lead in, achieving steady state levels of RPV, prior to the administration of RPV LA [Rashbaum, 2011a and Rashbaum, 2011b].

The selection of CAB 30 mg + ABC/3TC as an induction regimen is validated by clinical efficacy results from LAI116482. In addition, utilizing the same regimen, across all subjects, during the Induction Period will minimize the variability of responses between subjects, study complexity, and the impact of differential response rates during the Induction Period which could impact the interpretation of Maintenance Period results.

Maintenance Period

All subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period.

The objective of the Maintenance Period of this study is to assess the ability of a two-drug regimen of CAB LA and RPV LA to maintain virologic suppression for 96 weeks with the primary endpoint occurring after 32 weeks. Two injectable IM dosing regimens (Q8W and Q4W) and one oral control dosing regimen will be evaluated.

Subjects eligible to enter the Maintenance Period will be randomized 2:2:1 at Day 1 to one of the dosing regimens described below:

- CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
  - + Loading Dose of CAB 800 mg at Day 1
  - + Loading Dose of CAB 600 mg at Week 4
- CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
  - + Loading Dose of CAB 800 mg at Day 1
- CAB 30 mg + ABC/3TC once daily

Randomization will be stratified by HIV-1 RNA <50 c/mL before Week (-8) (yes or no).

Subjects on either IM regimen will discontinue the Induction regimen (including the add-on of RPV) after a final dose in the clinic on Day 1. Subjects on the oral regimen will discontinue the add-on of RPV after a final dose in the clinic on Day 1.

While both drugs, CAB LA and RPV LA, have been studied with both SC and IM administration, the IM administration is being progressed into study 200056 to best accommodate the required injection volumes of both drugs and to ensure good tolerability.

The selection of CAB 30 mg + ABC/3TC as an oral comparator regimen in this study, will allow for a direct comparison of subjects who either i) continue their existing regimen or ii) simplify their regimen to one of the IM regimens. The chosen comparator will also allow for a direct comparison of oral daily pill taking vs. Q4W and Q8W IM administration, as it relates to efficacy, tolerability, safety, and acceptability. Normalizing the comparator populations by randomizing only suppressed subjects at Day 1 will also serve to strengthen this comparison.

Long-term maintenance of HIV virologic suppression will be assessed.

Extension Period

The Extension Period of this study will allow for a collection of longer term efficacy and safety and tolerability data from subjects receiving CAB LA and RPV LA. Both of the current IM dosing regimens, Q8W and Q4W, will be taken into the Extension Period of the study based on similar efficacy results across each arm (see Section 1.8).

Unless subjects meet a study withdrawal criterion, subjects on the oral regimen may elect to continue on the Extension Period by switching to an optimized IM dosing regimen of their choice of CAB LA + RPV LA (either Q8W or Q4W).

Long-Term Follow-Up Period

Subjects who have received at least one dose of CAB LA and/or RPV LA are anticipated to be at high risk for development of virologic resistance if ART is interrupted. The time period during which subjects may be at greatest risk for developing virologic resistance may be the period between when drug levels fall below therapeutic exposures and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and may be dependent upon effective concentration, inhibitory concentration and half-life. Plasma concentrations of both drugs may be measurable for approximately 52 weeks following IM injections.

Therefore, any subject who receives at least a single dose of CAB LA and/or RPV LA and who discontinue the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. In this study, this will be accomplished through the Long-Term Follow-Up Period.

1.10. Dose Rationale

1.10.1. CAB

CAB 10 mg, 30 mg and 60 mg oral once daily achieved similar efficacy at Week 24 of Induction when coadministered with 2 NRTIs and at Week 48 of Maintenance (24 weeks on Maintenance) when coadministered with RPV 25 mg once daily (Table 1). Rates of virologic suppression through Week 48 (Maintenance) on the two drug regimen remained similar to that attained through Week 24 (Induction) on three-drug ART.

The oral dosing period intended for induction of virologic suppression also serves as a lead-in period required to confirm tolerability in each subject prior to initiating the prolonged exposure following CAB LA injection, which has been observed to be up to 52 weeks following a single injection in some subjects [GlaxoSmithKline Document Number RM2010/00170/04: LAI114433]. Although all doses provided similar induction and maintenance of viral suppression, CAB 30 mg once daily was selected as the oral dose to be used in combination with ABC/3TC for induction of virologic suppression in this study. CAB 30 mg achieves higher plasma exposures than the 10 mg oral dose, providing higher toxicity coverage prior to initiating IM dosing.

Based upon the results through Week 48 of the LAI116482 study, and in accordance with the pre-specified dose selection criteria at Week 24, a 30 mg oral dose of CAB has been selected to be used in combination with ABC/3TC for induction of virologic suppression in this study.

1.10.2. CAB LA

CAB 10 mg, 30 mg and 60 mg orally once daily achieved similar efficacy at Week 24 of Induction when coadministered with 2 NRTIs and at Week 48 of Maintenance (24 weeks on Maintenance) when coadministered with RPV 25 mg once daily (Table 1). Rates of virologic suppression through Week 48 (Maintenance) on the two drug regimen remained similar to that attained through Week 24 (Induction) on three-drug ART. The similar efficacy in all three treatment arms in LAI116482 suggests that maintaining target concentration at the end of a dosing interval (Cτ) following IM administration of CAB LA with RPV LA at approximately the level of the 10 mg oral dose (geometric mean 1.35 μg/mL, 8.1-fold above PA-90% inhibitory concentration [IC_{90}]) should also maintain suppression of HIV infection. Once safety and tolerability are confirmed with oral dosing, maintaining target Cτ following IM administration of CAB LA with RPV LA at approximately the level of the 10 mg oral dose (geometric mean 1.35 μg/mL, 8.1-fold above PA-IC_{90}) should be sufficient to maintain suppression of HIV infection. Maintaining a target at approximately the level of the 30 mg oral dose is not needed in Maintenance, as viral suppression and short-term tolerability have been established during Induction.

Using population pharmacokinetic (PK) modelling and simulations, CAB Cτ values for several IM dosing regimens were calculated and two regimens were selected based upon:

- ability to reach target concentration early in treatment,

- ability to maintain mean Cτ above that obtained with oral CAB 10 mg once daily during treatment (CAB trough concentrations ≥1.35 μg/mL), and
- minimizing the total number of injections per visit.

Table 1 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-E Population)

Visit	GSK744 10 mg N=60 n (%)	GSK744 30 mg N=60 n (%)	GSK744 60 mg N=61 n (%)	GSK744 Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Week 16 – Induction	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
Week 24 – Induction	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
Week 48 - Maintenance	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)

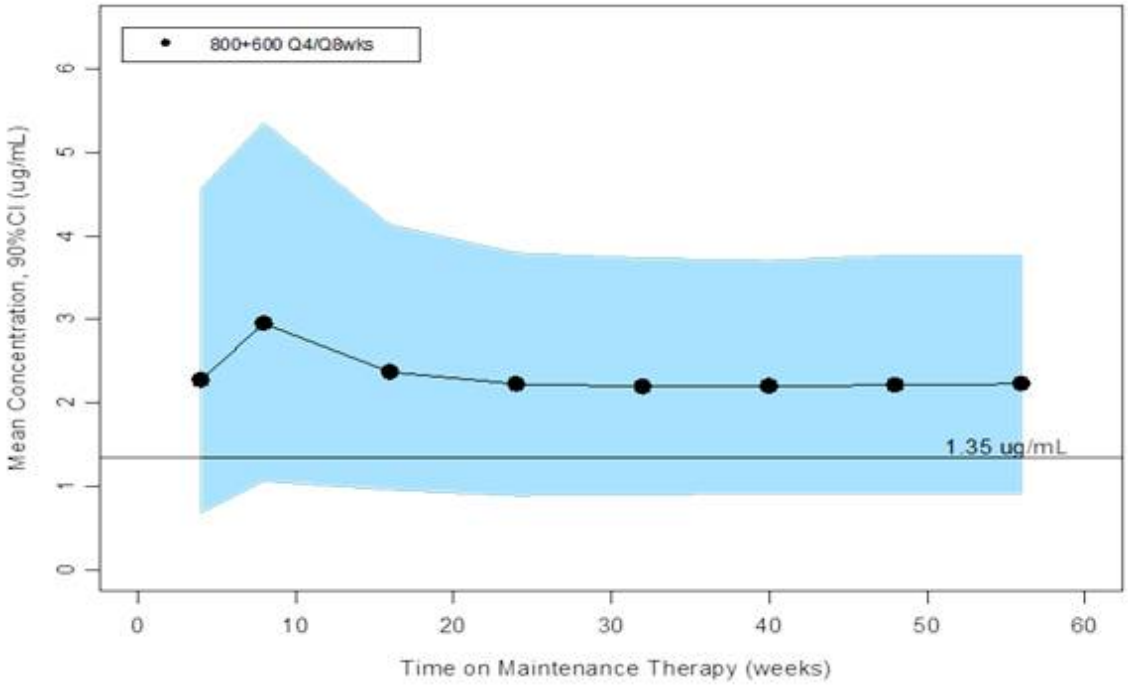
CAB LA– Maintenance Period

Q8W

Subjects randomized to CAB LA Q8W will receive a CAB 800 mg IM Loading Dose on Day 1 (within 2 hours of final oral dosing), a 600 mg IM Second Loading Dose at Week 4, and 600 mg IM Q8W starting at Week 8.

The first 800 mg IM loading dose and second 600 mg IM loading dose were selected so that ≥80% of subjects will be above 1.35 μg/mL throughout treatment. Mean (90% confidence interval [CI]) simulated CAB Cτ values versus time across doses for CAB LA Q8W are presented graphically in Figure 1.

Figure 1 Simulated Mean (90% CI) CABTrough Concentrations versus Time for CAB LA Q8W



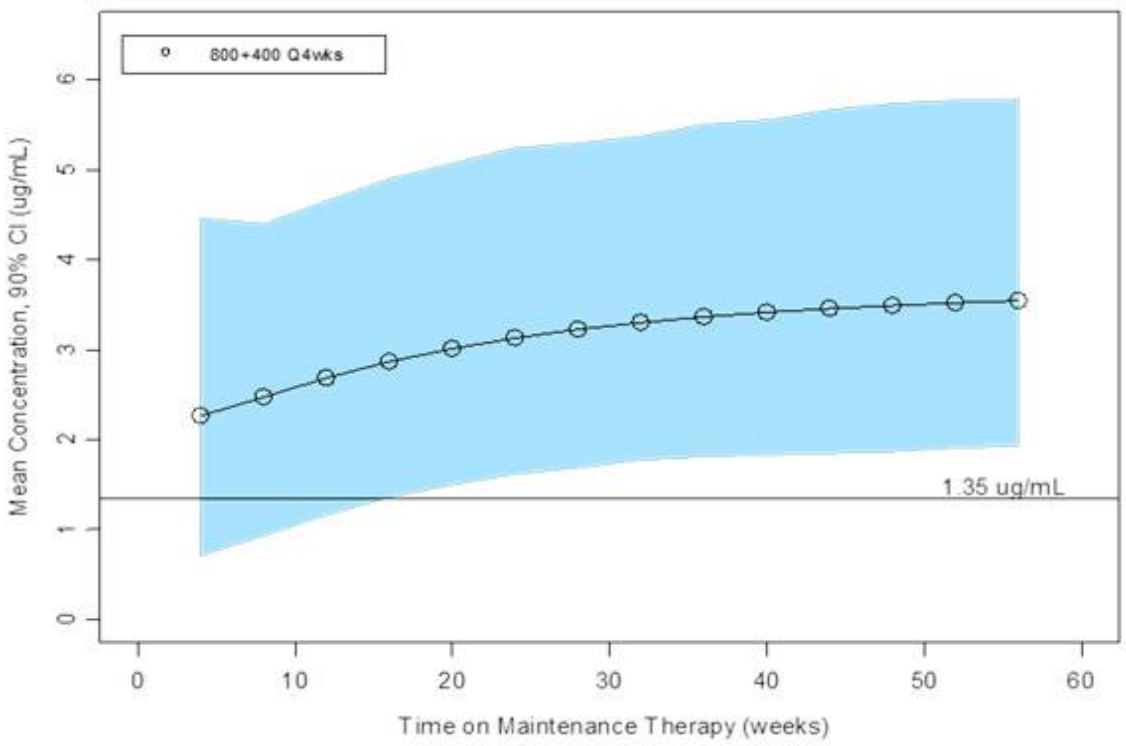
At Week 56 (approximately one year of dosing), CAB LA Q8W is predicted to achieve CAB trough concentrations ≥1.35 µg/mL (target) in 84% of subjects. Although the lower bound of the 90% CI falls below 1.35 µg/mL, Cτ for all subjects remains above 4•PA-IC_{90} (0.166 µg/mL). At Week 56, geometric mean CAB Cτ for CAB LA Q8W is predicted to be 2.02 µg/mL, 1.5-fold above target and 12.2-fold above PA-IC_{90} (Table 2).

A one week delay in dosing at steady state the Q8W regimen is predicted to result in a geometric mean Cτ that is 9% lower than for dosing that is administered on schedule while remaining above the 1.35 µg/mL target associated with the 10mg oral dose.

Q4W Subjects randomized to the Q4W dosing arm will first receive CAB 800 mg IM as a loading dose on Day 1 (within 2 hours of final oral dosing) and then, starting at Week 4, will receive CAB 400 mg IM Q4W.

The 800 mg loading dose was selected so that ≥80% of subjects will be above 1.35 µg/mL throughout treatment, including the end of the first dosing interval. Mean (90% CI) simulated CAB Cτ values versus time across Q4W doses for CAB LA are presented graphically in Figure 2.

Figure 2 Simulated Mean (90% CI) GSK744 Trough Concentrations versus Time for CAB LA Q4W



At Week 56 (approximately one year of dosing), CAB LA Q4W is predicted to achieve CAB trough concentrations ≥1.35 µg/mL (target) in 99.6% of subjects. Geometric mean CAB Cτ for CAB LA Q4W at Week 56 is predicted to be 3.35 µg/mL, 2.5-fold above target, 20.2-fold above the PA-IC_{90} (0.166 µg/mL), and similar to the observed mean Cτ after 16 weeks of this regimen in healthy subjects (Table 2).

A one week delay in dosing at steady state for the Q4W regimen is predicted to result in a

geometric mean Cτ that is 8% lower than for dosing that is administered on schedule while remaining above the 1.35µg/mL target associated with the 10 mg oral dose.

Table 2 Summary of Cabotegravir PK Parameters following oral administration in HIV infected subjects, CAB LA administration in healthy subjects, and following Simulations

Route Study Population	CAB Regimen	CAB PK Parameter			
		Cτ or C0 (μg/mL)[a]	Cmax (μg/mL)[b]	AUC(0-τ) (μg• h/mL)[c]	IQ (C0:IC_{90} ratio)[d]
Oral LAI116482 HIV	10 mg orally every day	1.35 [45%]	2.77 [33%]	45.7 [32%]	8.13
	30 mg orally every day	4.20 [40%]	7.49 [28%]	134 [32%]	25.3
	60 mg orally every day	7.93 [39%]	13.1 [44%]	195 [48%]	47.8
IM LAI115428 HVs	800 mg IM LD 400 mg IM Q4W x3	3.22 [28%]	4.37 [33%]	2362 [27%]	19.4
IM PopPK simulation HIV	LA Regimen #1 (200056): 800mg IM LD 400mg IM Q4W from W4	3.35 [35%]	ND	ND	20.2
IM PopPK simulation HIV	LA Regimen #2 (200056): 800mg IM LD 1 600mg IM LD 2 (Week 4) 600mg IM Q8W from W8	2.02 [52%]	ND	ND	12.2

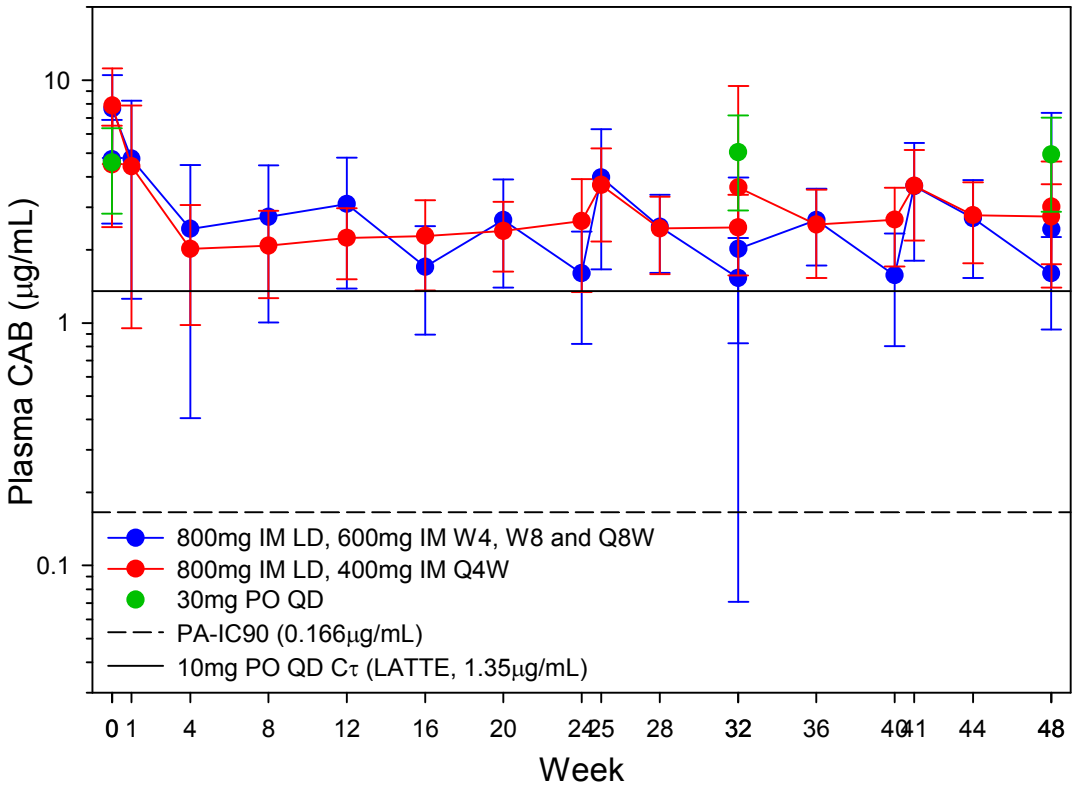
Data presented as Geometric mean [CVb%], HIV = HIV infected subjects, HV = Healthy Volunteers, ND=Not determined, LD = Loading Dose

a. C0: n=57 (10 mg orally), 53 (30 mg orally), 55 (60 mg orally), 9 (800 mg/400 mg IM),
b. Cmax: n=14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
c. AUC(0-τ): n=14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
d. PA-IC_{90} determined in vitro 0.166 μg/mL.

CAB LA – Extension Period

CAB concentrations following administration of CAB LA Q8W and Q4W during the Maintenance Period of LATTE-2 were lower than predicted by the modelling and simulation in the original protocol. Observed data for both CAB LA regimens in LATTE-2 are presented in Figure 3. The CAB LA population PK model has been updated to include data from Phase 2a/b studies, specifically Study 201120 (CAB LA PrEP) and Study 200056. The current model has increased from 93 subjects to 416 subjects receiving CAB LA single or repeat IM injections. The rationales for the new CAB LA IM dosing regimens are described below.

Figure 3 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 48 (200056, LATTE-2)

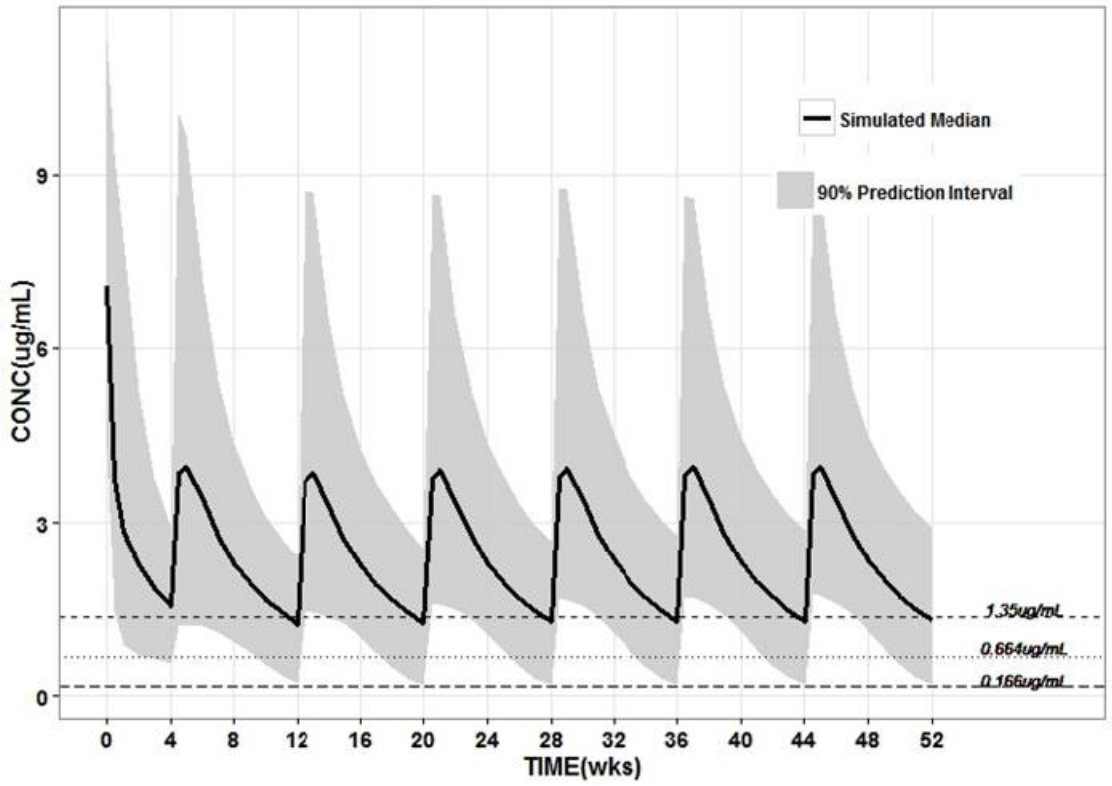


Both predose and 2h post injection concentrations are shown at Time Zero, Week 32, and Week 48.

Extension Phase Rationale for CAB LA Q8W

After the Maintenance Period oral regimen, the first and second CAB LA 600 mg IM dose at study visit Week 100 (1st injection day) and Week 104 (2nd injection) of the Extension Period of this study was selected so that 50% of subjects are anticipated to be above 1.35 µg/mL, the geometric mean Cτ following oral CAB 10 mg once daily, throughout treatment which was shown to be efficacious in the LATTE study. The lower bound of the 90% prediction interval is approximately 0.166 µg/mL, indicating that 95% of subjects on this regimen should remain above the PA-IC_{90} throughout dosing (Figure 4).

Figure 4 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, Q8W thereafter)^

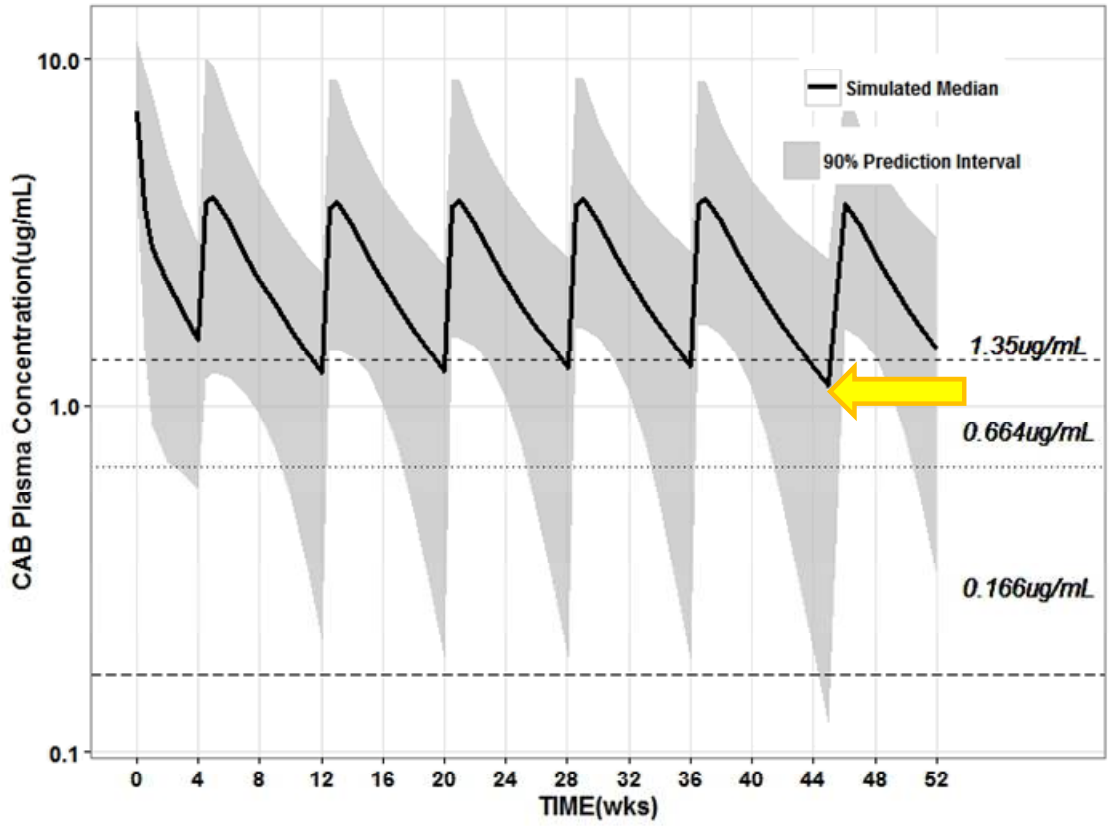


*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Model based predicted steady-state CAB concentrations were consistent with observed data in this study, where CAB LA 600 mg IM Q8W was given, albeit with a loading dose of 800 mg IM on Day 1 and a third dose of 600 mg IM at Week 8 prior to initiating Q8W. The mean CAB plasma concentration at Week 32 was 1.53 μg/mL (Figure 3).

At steady state, a one week delay in dosing of the Q8W regimen is predicted to result in a median steady state Cτ that is 15% lower than for dosing that is administered on schedule, with 92% remaining above the PA-IC_{90} (Figure 5).

Figure 5 **Impact of 1-week Delay in Dosing at Steady State (Week 44) on Simulated* Median (90% PI) CAB Plasma Concentrations versus Time for the Optimized CAB LA 600 mg IM Q8W regimen (Day 1, Week 4, and Q8W thereafter^)**

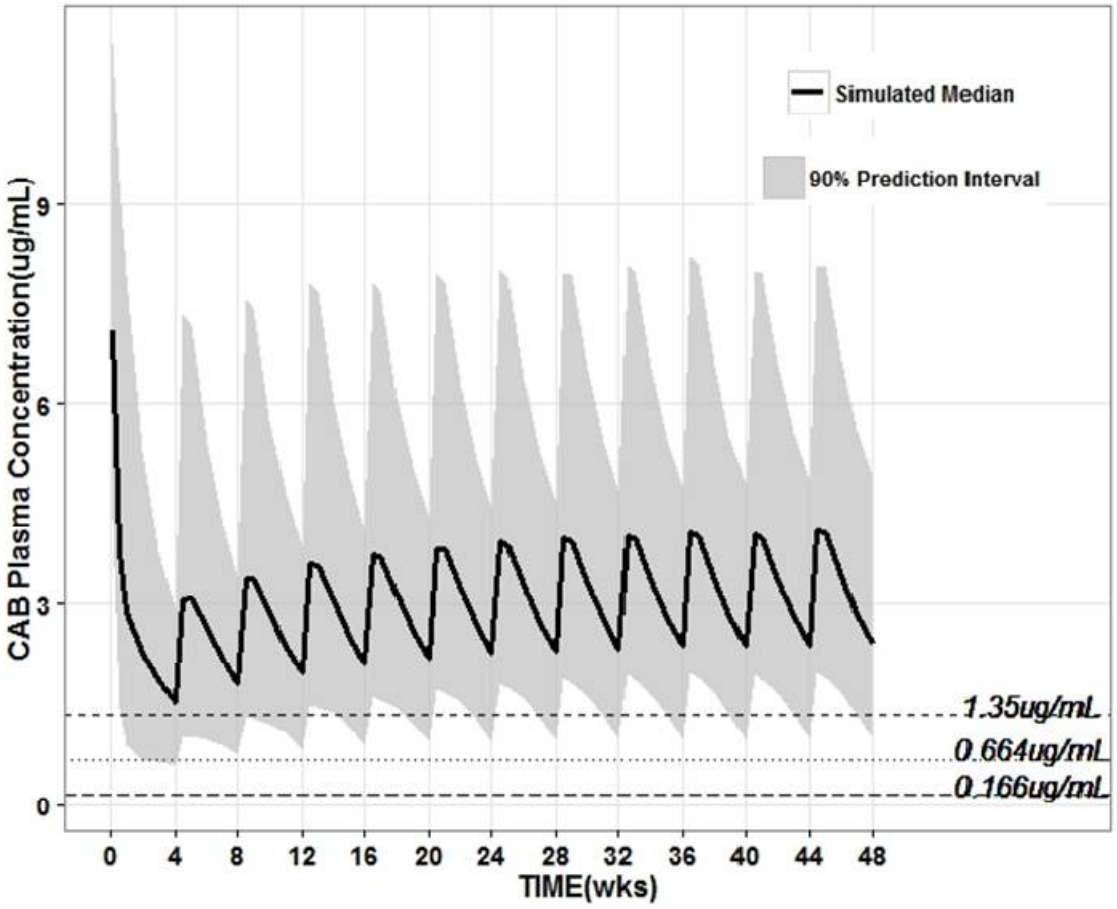


*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Extension Phase Dose Rationale for CAB LA Q4W

The simulation of the predicted median (90% prediction interval [PI]) CAB concentration-time profile based on the population PK model is shown in Figure 6. The lower bound of the PI remains approximately at or above 4x PA-IC_{90} throughout dosing. At steady state, 98% of the population is predicted to achieve trough concentrations above 4x PA-IC_{90}, and 88% is predicted to achieve trough concentrations above the geometric mean trough following the 10 mg oral dose in LATTE of 1.35 µg/mL (8x PA-IC_{90}).

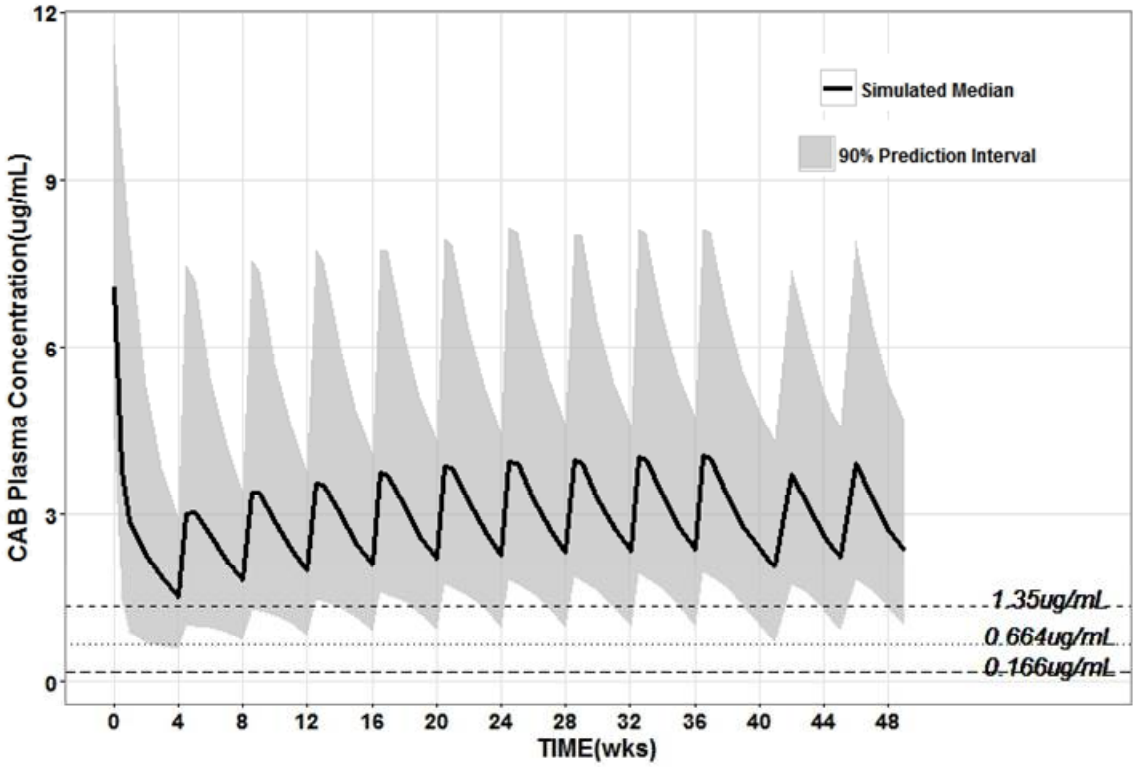
Figure 6 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q4W Regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Ctrough concentration following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC_{90}
Long dashed line at 0.166 μg/mL corresponds to the PA-IC_{90}.

At steady state, a one week delay in dosing of the Q4W regimen results in approximately 15% reduction in median CAB trough. With this delay, 95% are predicted to remain above 4x PA-IC_{90}, and 79% are predicted to remain above the 10 mg oral target (Figure 7). Simulations including delays greater than one week have been explored (not shown), with <70% of subjects remaining above the 10 mg oral target. Therefore, a 1-week delay is the maximum allowed per the protocol.

Figure 7 Impact of 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q4W regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Cτ following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC_{90}
Long dashed line at 0.166 μg/mL corresponds to the PA-IC_{90}.

1.10.3. RPV

All subjects will receive 4 weeks of RPV 25 mg once daily, co-administered with CAB+ABC/3TC, from Week (-4) through Day 1 to confirm tolerability in each subject prior to possible IM dosing with RPV LA. Data from study LAI116182 [GlaxoSmithKline Document Number 2012N134026_02: LAI116482] have demonstrated that there is no clinically relevant drug-drug interaction following repeat oral administration of CAB with RPV. With this oral RPV add-on, subjects will also have steady-state RPV plasma concentrations prior to starting CAB LA dosing during the Maintenance Period.

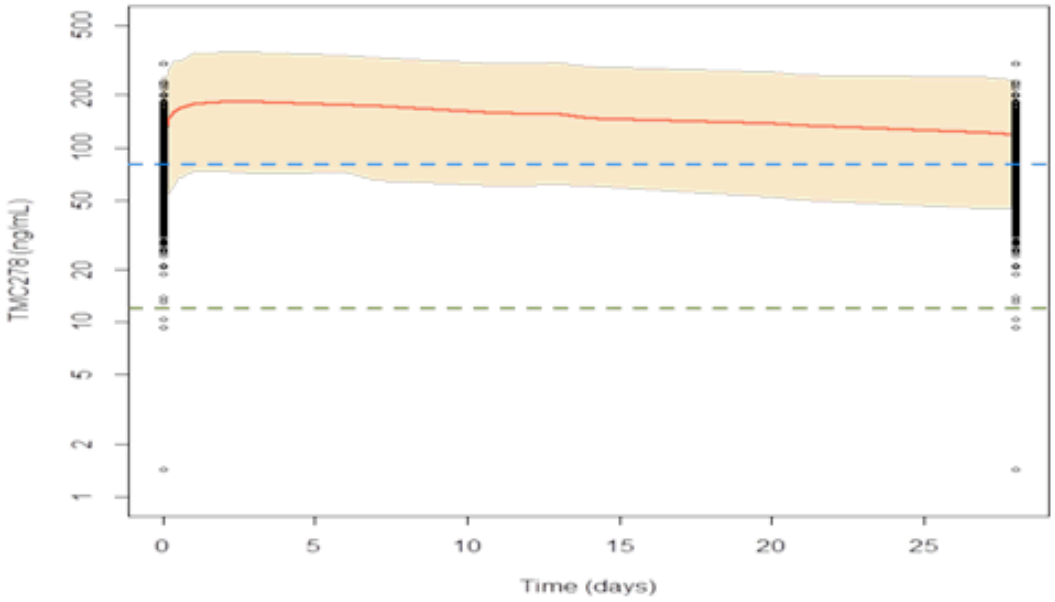
1.10.4. RPV LA

During the Maintenance Period, subjects will receive either IM injections of CAB LA 600 mg every 4 weeks (Q4W) or RPV LA 900 mg every 8 weeks (Q8W). The selection of the RPV LA dosing regimens is based on achieving RPV plasma concentrations in the range of those observed with oral RPV 25 mg once daily in HIV-infected patients (mean (SD) C_{trough} of 80 (36) ng/mL in pooled Phase III studies (RPV + 2 NRTIs); and 77 (34) ng/mL in the Maintenance Phase of LAI116482 (RPV + CAB), as well as constructing a regimen that is most practical for patients, i.e. by reducing the number of dosing/clinic visits while maintaining an acceptable injection volume.

Figure 8 and Figure 9 show the model-predicted RPV plasma concentrations over a dosing interval at steady-state with the respective Q4W and Q8W RPV LA dosing regimens. The graphs show the mean profile (red curve) with the 90% prediction interval (shaded area). Also indicated are the mean C_{trough} for oral RPV 25 mg once daily in HIV-infected patients (Phase III, 80 ng/mL) and the protein-binding adjusted IC_{90} for RPV (12 ng/mL), as well as a scatter of the individual C_{trough} values (plotted both at the beginning and at the end of the RPV LA dosing interval) in HIV-infected patients (Phase III).

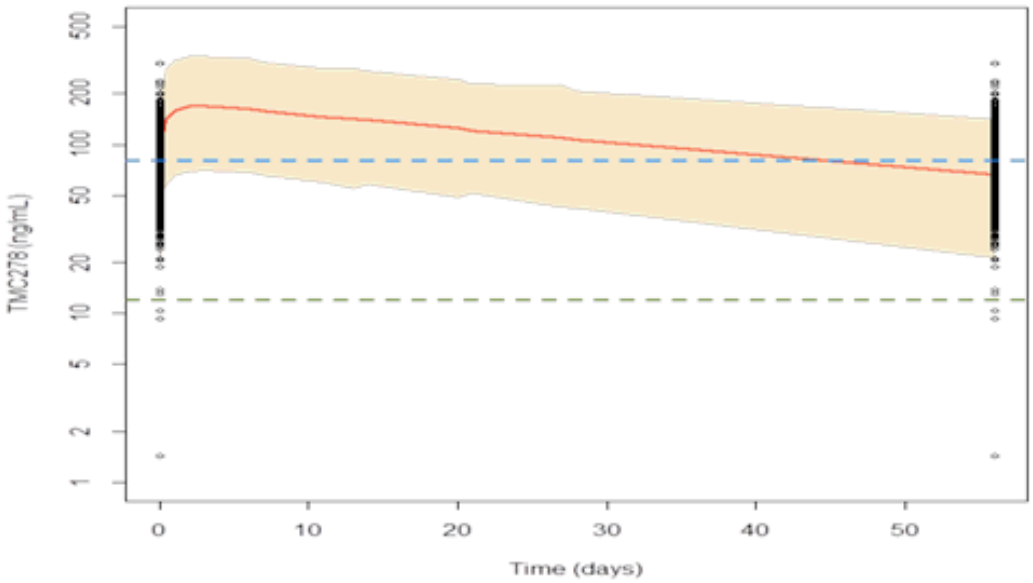
For the simulations, a pharmacokinetic model was used based on all available data from studies with the current RPV LA formulation (TMC278-C158, SSAT040, LAI115428) and the population PK model of RPV. With this model, the RPV LA dosing regimen (i.e., 4 weeks RPV 25 mg every day followed by IM injections every 4 weeks of RPV LA 600 mg) was simulated for 100 subjects. For each of these individuals, the median Ct between day 168 (i.e. after injection 5) and day 336 (i.e., after injection 11) was determined, and from these median values, the mean across subjects was calculated [GlaxoSmithKline Document Number 2011N112455_03: LAI115428].

Figure 8 **Model-Predicted Mean (90% prediction interval) RPV Plasma Concentration-Time Profile at steady-state after Q4W IM injections of RPV LA 600 mg (immediately following 4 weeks oral RPV 25 mg once daily)**



Red line represents the predicted mean steady state C_{trough} concentration.
Blue dotted line represents mean C_{trough} for oral RPV 25 mg once daily;
Green dotted line represents protein-binding adjusted IC_{90} for RPV;
Black open circles represent individual C_{trough} values with oral RPV 25 mg once daily

Figure 9 Model-Predicted Mean (90% prediction interval) RPV Plasma Concentration-Time Profile at steady-state after Q8W IM injections of RPV LA 900 mg (immediately following 4 weeks oral RPV 25 mg once daily)



Red line represents the predicted mean steady state C_{trough} concentration.
Blue dotted line represents mean C_{trough} for oral RPV 25 mg once daily;
Green dotted line represents protein-binding adjusted IC_{90} for RPV;
Black open circles represent individual C_{trough} values with oral RPV 25 mg once daily

RPV LA – Maintenance Period

Q8W

For the Q8W RPV LA dosing regimen, the mean steady-state C_{trough} is predicted to be around 65 ng/mL, as of the 1st injection. Though this is below the mean RPV C_{trough} with oral RPV 25 mg once daily, the range of model-predicted C_{trough} is similar to the range of C_{trough} with oral RPV 25 mg once daily in the RPV Phase III studies (Figure 9) and in LAI116482 (Maintenance). The RPV plasma concentrations are also higher during the larger part of the RPV LA dosing interval. Furthermore, all patients are virologically suppressed before switching to the RPV LA regimen. In LAI116482, there were 58/160 HIV-infected patients with a RPV C_{trough} (based on population PK modeling) below 65 ng/mL. These 58 patients all maintained virologic suppression.

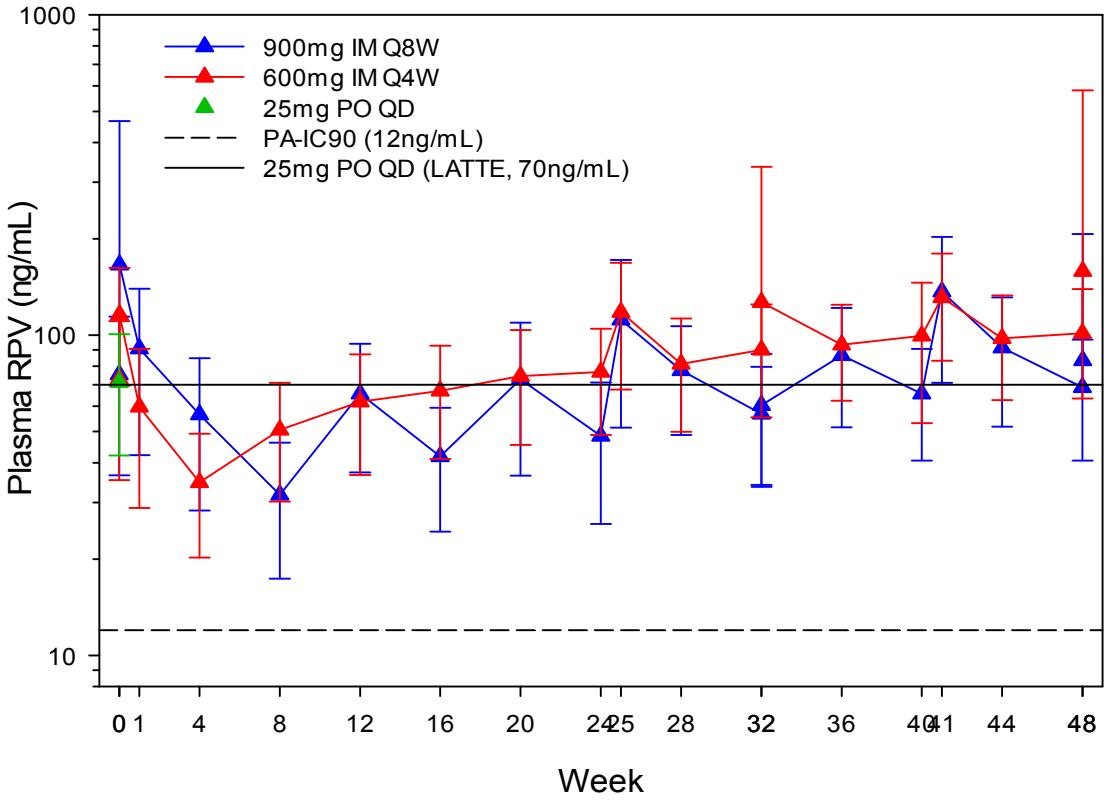
Q4W

The mean steady-state C_{trough} with the Q4W RPV LA dosing regimen is predicted to be around 115 ng/mL. This is above the mean RPV C_{trough} (80 ng/mL) and the mean C_{avg} (100 ng/mL) for RPV 25 mg once daily (Phase III). Furthermore, the mean RPV plasma concentrations are already above the mean C_{trough} for RPV as of the 1st injection with RPV LA 600 mg.

RPV LA – Extension Period

Similar to CAB, RPV concentrations following RPV LA in LATTE-2 were lower than predicted by the modelling and simulation in the original protocol. Observed data for both RPV LA regimens in LATTE-2 are presented in Figure 10. The RPV LA population PK model has been updated to include data from LATTE-2.

Figure 10 Observed Mean (SD) Concentration-Time Data following RPV LA Q8W and Q4W through Week 48 and Day 1 Cτ following RPV 25 mg PO QD (LATTE-2)



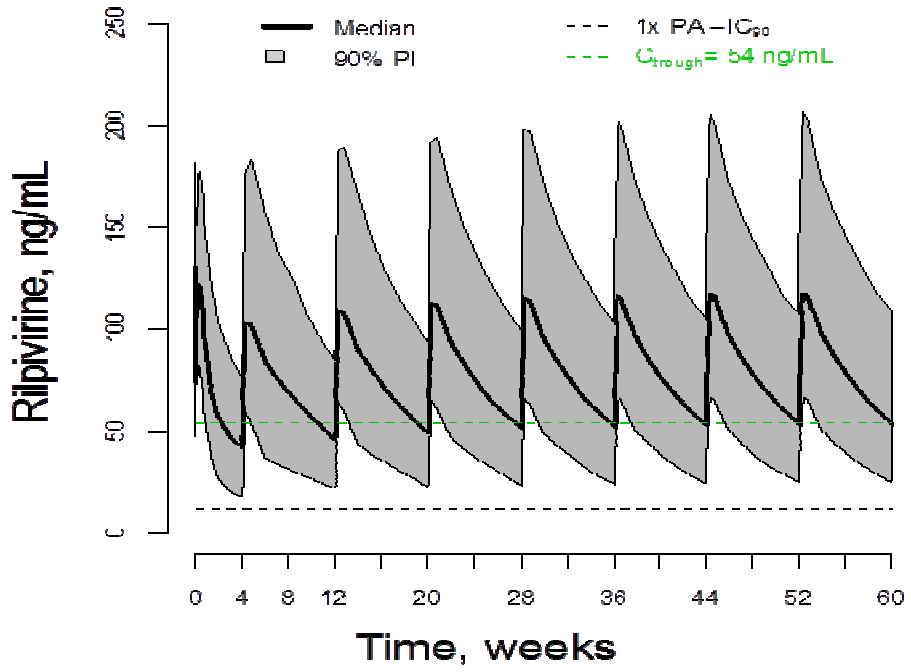
Extension Phase Rationale for RPV LA Q8W

The new optimized RPV LA Q8W regimen for this study was selected based on safety and efficacy data from this study, 200056 (LATTE-2) and supported by modelling and simulation of pharmacokinetic and response data obtained following administration RPV LA administration in healthy subjects (Phase 1 studies C158 and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected subjects (Phase 2 study LATTE-2), the majority of the data coming from 200056 (LATTE-2).

The predicted median (90% PI) steady-state Cτ for the optimized RPV LA Q8W regimen is 54 ng/mL (25 – 109 ng/mL) (Figure 11). With this regimen, 100% of subjects remain above the RPV PA-IC_{90} during the whole dose interval at steady-state. These data are similar to the observed Week 32 median steady-state Cτ which was also 54 ng/mL and the mean Cτ was 58 ng/mL (Figure 10). With the 2nd RPV LA dose at Week 104, the anticipated median RPV Cτ at Week 104 is 42 ng/mL (versus 30 ng/mL observed prior to

second injection at Week 8 in LATTE-2), with >98% of subjects above the RPV PA-IC_{90}.

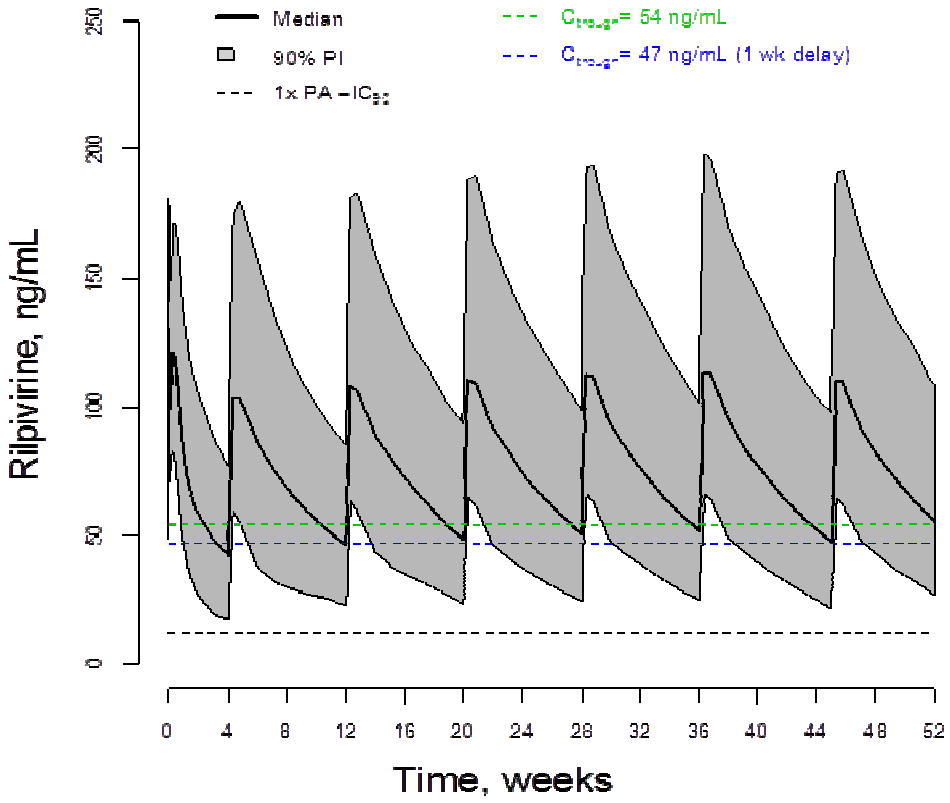
Figure 11 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q8W regimen (900 mg IM Day 1, Week 4, and Q8W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

At steady-state, a one week delay in dosing for the Q8W regimen is predicted to result in a median steady-state Cτ that is approximately 13% lower (47 ng/mL) than for dosing that is administered on schedule, with >99% of subjects still remaining above the RPV PA-IC_{90} (Figure 12). This supports allowance of some flexibility in the dosing regimen in this study, similar to what is currently practiced in this study.

Figure 12 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for Optimized RPV LA Q8W dosing regimen, impact of 1-week visit window (injection at Week 45 instead of Week 44)^



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

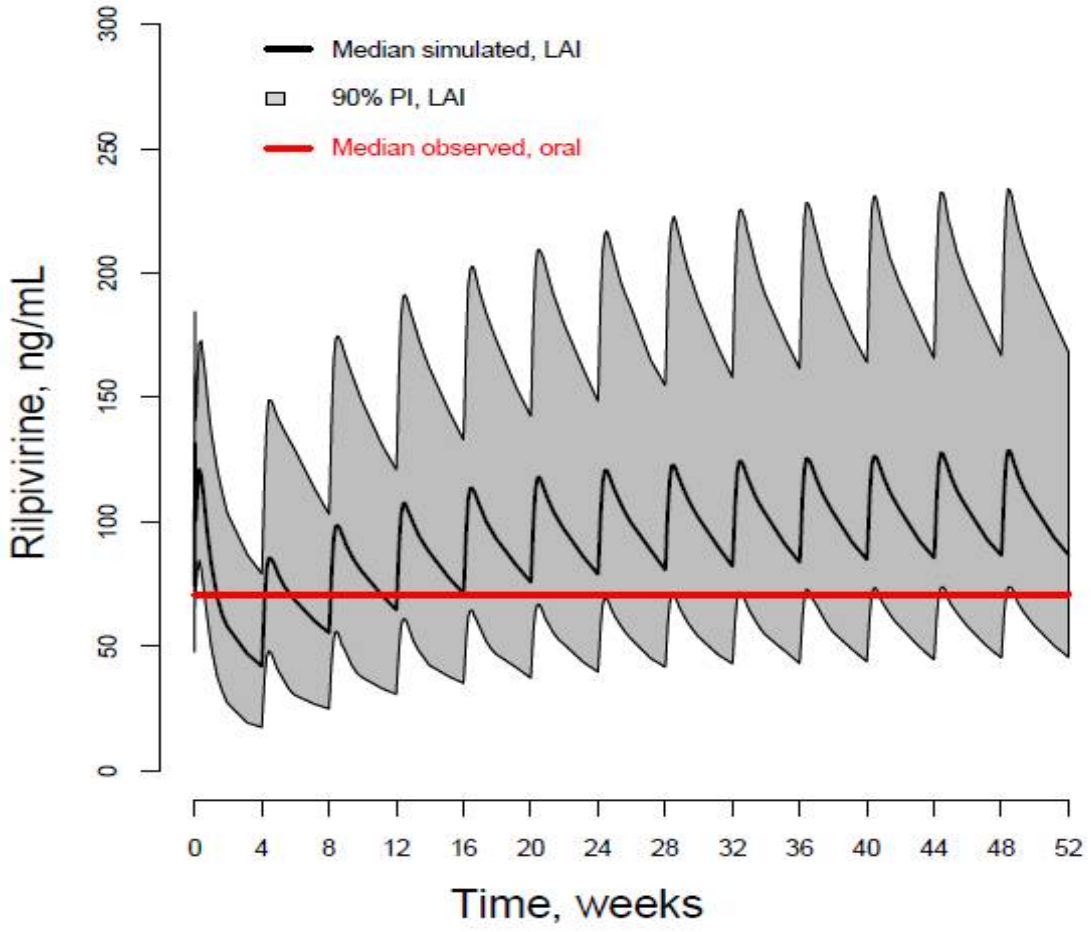
Extension Phase Rationale for RPV LA Q4W

The optimized RPV LA Q4W regimen for this study was selected based on LATTE-2 safety and efficacy data as described above and supported by modeling and simulation of pharmacokinetic data obtained following administration of RPV LA in healthy participants (Phase 1 studies C158 and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected participants (Phase 2 study LATTE-2), with the majority of the data coming from 200056 (LATTE-2).

The predicted median (90% PI) steady-state Cτ for the proposed regimen is 86.8 ng/mL (45.6 – 168 ng/mL) (Figure 13). With this regimen, >99% of participants remain above the 5th percentile of steady state trough values following oral RPV 25 mg (corresponding to 2x the PA-IC_{90}). With a loading dose of 900 mg RPV LA on Day 1, the anticipated

median RPV Cτ at Week 4 is 42 ng/mL, with >98% of participants above the RPV PA-IC_{90}.

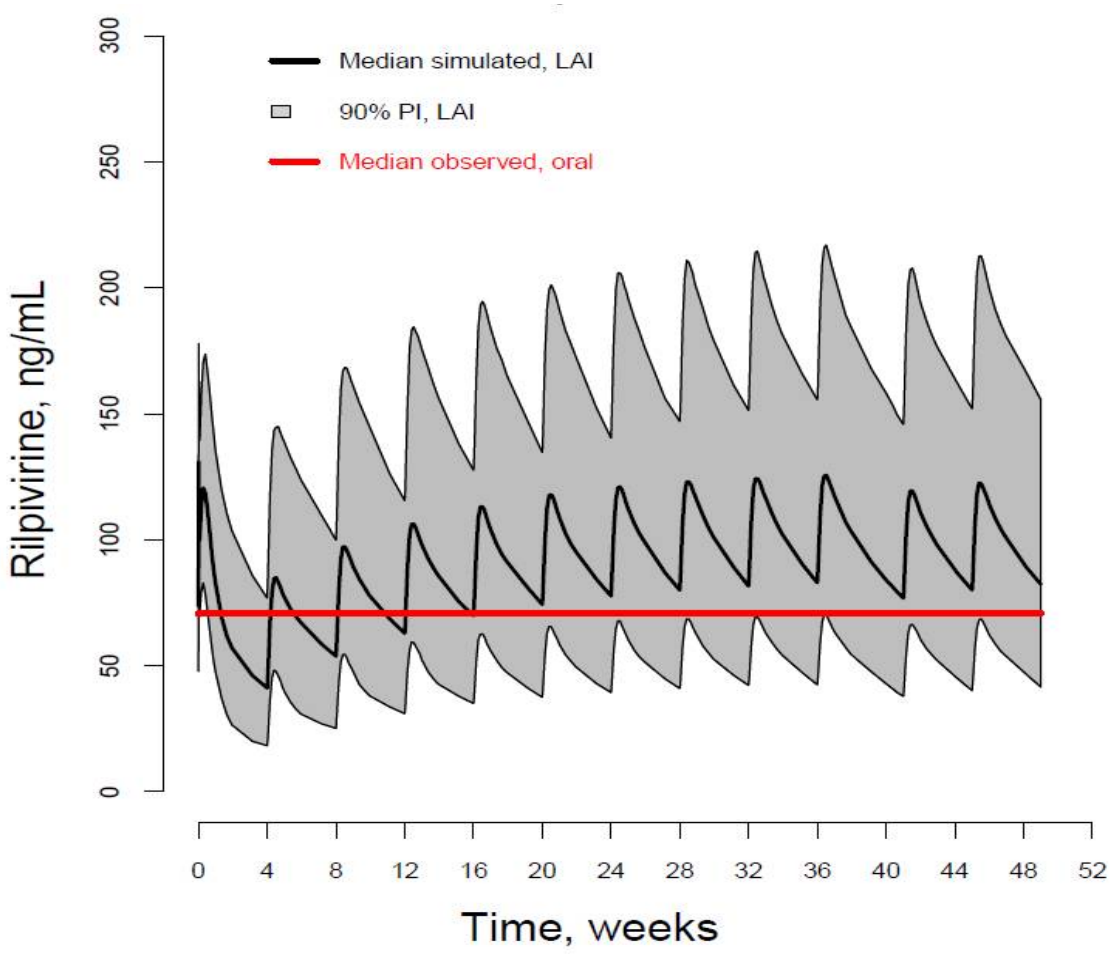
Figure 13 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q4W regimen (900 mg IM Day 1, then 600 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Horizontal line at 72 ng/mL corresponds to median Cτ following oral RPV 25mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV Cτ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

At steady-state, a one week delay in dosing for the Q4W regimen is predicted to result in a median steady-state Cτ that remains above the median trough for RPV 25 mg (Figure 14). This supports allowance of some flexibility in the dosing regimen.

Figure 14 Impact of 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) RPV Plasma Concentrations versus Time for Optimized RPV LA Q4W dosing regimen (900 mg IM Day 1 and then 600 mg IM Q4W thereafter^)



*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Horizontal line at 72 ng/mL corresponds to median $C\tau$ following oral RPV 25 mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV $C\tau$ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

1.11. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with CAB and CAB LA can be found in the Investigator's Brochure. RPV is a recently authorized medicinal product and detailed information on its benefit/risk profile together with any risk mitigation measures are described in product labeling. Summaries of findings from both clinical and non-clinical studies conducted with RPV LA can be found in the Investigator's Brochure. Other medicinal products including ABC/3TC that are administered in this protocol have been in clinical use for at least 10 years and have well established benefit/risk profiles described in detail in their respective product labels.

Relevant mitigation measures are also incorporated in to this protocol. The following sections outline the risk assessment and mitigation strategies specific to this protocol:

1.11.1. Risk Assessment

1.11.1.1. CAB and CAB LA

Since CAB is at an early stage of clinical development, and exposure in humans with or without HIV infection is limited, the clinical safety profile in humans has yet to be fully elucidated. The following risks have primarily been identified during routine preclinical testing and/or in the clinical trial experience to date and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about the clinical experience to date and possible risks associated with treatment using CAB can be found in the Summary of Data and Guidance for the Investigator section of the IB.

Elevated Liver Transaminases

A small proportion of participants in the CAB program to date (total exposure approximately 1198 to 01 April 2016) have developed transaminitis (elevated liver transaminases characterised by predominant ALT elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection and whilst a small number of others did not have alternative explanations, suggesting a mild form of DILI (drug induced liver injury) without hepatic dysfunction which resolved upon withdrawal of treatment with CAB.

Of the five participants with possible or probable cases of DILI identified in Phase 2 studies, four participants were receiving oral CAB and one participant developed probable DILI following CAB LA or Placebo LA administration.

Mitigation: Liver transaminases will be closely monitored throughout this study (refer to Time & Events Table) and the liver chemistry stopping criteria will be adopted as described in Section 6.10.3.1 of this protocol. All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. This risk will also be mitigated by exclusion criteria as described in Section 4.3. In addition, an oral lead in period is being implemented in this study, where all subjects will receive CAB oral during the Induction Period, to determine individual safety and tolerability, prior to the possible administration of CAB LA.

Elevated Serum Creatinine

This risk was identified from placebo controlled studies which demonstrated slightly more pronounced changes from Baseline associated with CAB exposure compared to placebo. Changes were generally small with a maximum change from Baseline observed at a dose of 30 mg given to 12 healthy subjects for 24 days (~ 0.19 mg/dL at Day 24), Levels returned to Baseline after cessation of CAB dosing. Further Phase I and Phase II clinical studies have not demonstrated an increase in creatinine levels with CAB administration. No pre-clinical signal for renal toxicity has been demonstrated and

findings in humans have not been associated with clinically evident renal dysfunction or proteinuria.

Mitigation: Standard renal toxicity monitoring procedures and treatment stopping guidelines for CAB are incorporated in to this protocol as described in Section 6.10.6.9.

Creatine Phosphokinase (CPK) elevations

Occurrences of asymptomatic, transient instances of elevations of CPK levels have been observed in Phase I studies and an ongoing Phase IIb studies with CAB at dose levels of 10, 30 and 60 mg (LAI116482) and with CAB LA (200056). These generally appeared to be related to physical activity, were not associated with clinical symptoms and returned to pre-treatment levels in all cases. No subject has required a discontinuation of CAB as a result of a CPK elevation. Rhabdomyolysis of uncertain cause has been included in labeling for a currently available integrase inhibitor (raltegravir) but has not been seen in any subject receiving CAB to date.

Mitigation: standard laboratory monitoring as detailed in Section 6.10.6.7. Occurrences of elevated CPK levels will be reported and managed as described in Section 6.10.6.7.

Bone Marrow depletion

This risk was demonstrated in high dose (1000 mg/kg/day) CAB monkey study but was not apparent from studies conducted in rats or at lower dose levels in monkeys. Blood disorders such as anemia and leucopenia are labeled for other drugs of the integrase inhibitor class. No signal for bone marrow depletion has been identified for CAB to date through Phase IIb.

Mitigation: Doses used within this study will result in many fold lower level exposure compared to the effect level in primates. Careful monitoring of adverse hematological events (including laboratory monitoring as in Section 6.10.2) will occur during study conduct. Serious/severe events will be managed appropriately including, but not limited to, withdrawal of CAB, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

Gastrointestinal intolerability

The risk identified in a monkey toxicity study at the highest administered dose of CAB and considered related to local irritation (rather than a systemic effect) leading to morbidity associated with clinical signs of intolerance.

Mitigation: Careful monitoring of adverse GI events will occur throughout the study. Serious/severe events will be managed appropriately including, but not limited to, withdrawal of CAB, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

Injection Site Reactions

The occurrence of ISRs was identified in rats and monkeys at all dose levels of CAB LA and associated with both the IM and SC route of administration. In humans, experience to date has demonstrated ISRs occur in the majority of exposed subjects but are generally mild (Grade 1) or moderate (Grade 2) and include tenderness, erythema, or nodule formation of several days duration. Reactions have been well tolerated and have only rarely led to subject withdrawal.

Mitigation: Subjects will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. Specialist dermatology consultation will be sought if warranted for individual subjects.

Hypersensitivity Reactions (HSR)

While there have been no clinical cases of hypersensitivity to CAB, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of CAB LA. The long exposures anticipated after a CAB LA injection may complicate the management of a drug hypersensitivity reaction, were it to occur.

Mitigation: This risk of developing a hypersensitivity reaction post administration of CAB LA will be minimized by the use of an oral lead-in of CAB to determine individual safety and tolerability prior to the introduction of CAB LA. Any reactions would be managed supportively.

Development of Resistance

Residual concentrations of CAB would remain in the systemic circulation of participants for prolonged periods (up to 1 year) despite stopping treatment (e.g. for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy.

Mitigation: Alternative oral HAART regimens will be prescribed within four weeks after participants stop CAB LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing of the risk of emergent resistance. The participants in this study who discontinue CAB LA for any reason will be monitored for a minimum of 52 weeks from the time of the last CAB LA injection.

Drug-Drug Interactions (DDIs)

Residual concentrations of CAB would remain in the systemic circulation of subjects who stopped treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (months). Subjects discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy. Of note, evidence to date indicates that significant DDIs with CAB and other antiretrovirals are unlikely to occur.

Mitigation: None needed at this time. All subjects will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of CAB. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Mitigation: Training will be provided to all sites on proper injection technique. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a PK sample, post dose ECG, vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the Medical Monitor notified. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV concentrations.

1.11.1.2. RPV and RPV LA

For safety and risk mitigation for RPV, refer to the rilpivirine prescribing information [Edurant Product Information, 2015]. Information about the clinical experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB. Beyond what has already been identified with oral RPV, no new systemic adverse reactions to RPV LA (same active moiety) have been observed. The following risks are considered to be of specific clinical relevance in the context of IM use:

Injection Site Reactions

Injection site pain (upon touch) mild to moderate and injection site induration have occurred with RPV LA injection. Incidences vary with dose (volume of administration) and site of injection. Any recurrence may be linked to the formulation used and any recurrence will be monitored in future repeated dose clinical studies with RPV LA.

Mitigation: Local tolerance will be closely monitored.

Rash

Some observations of rash with RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2).

Mitigation: In this study, RPV LA administration will be preceded by a one month RPV lead in to evaluate safety and tolerability in individual participants.

Development of Resistance

Residual concentrations of RPV LA would remain in the systemic circulation of subjects who stopped treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (months). Participants discontinuing a LA regimen may be at risk for developing resistance to RPV many weeks after discontinuing injectable therapy.

Mitigation: Alternative oral HAART regimens will be constructed for subjects stopping long acting therapy which would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimization of the risk of emergent resistance. The Sponsor will continue to monitor subjects in this study who discontinue a LA regimen for any reason for a minimum of 52 weeks from the time of the last LA administration.

Drug-Drug Interactions (DDIs)

Residual concentrations of RPV would remain in the systemic circulation of subjects who stopped treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (months). Subjects discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy. Of note, evidence to date indicates that significant DDIs with RPV LA and other antiretrovirals are unlikely to occur.

Mitigation: None needed at this time. All subjects will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.

Refer to the Investigator Brochure for RPV LA for detailed descriptions of the clinical experience to date [TMC278 LA [Rilpivirine, oral and parenteral] Integrated Investigator's Brochure, 2016].

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that RPV LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of RPV LA. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with RPV LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Mitigation: Training will be provided to all sites on proper injection technique. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a PK sample, post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the Medical Monitor notified. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV concentrations.

1.11.1.3. Abacavir/Lamivudine (ABC/3TC)

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of HLA-B*5701 and subsequently avoiding ABC in HLA-B*5701 positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were HLA-B*5701 negative and who received ABC developed a clinically suspected ABC HSR, respectively.

In any subject treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ZIAGEN™, EPZICOM/KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the Local Country Prescribing Information for EPZICOM.

Mitigation: Every potential subject will be screened for the carriage of the HLA-B*5701 allele. Subjects who are HLA-B*5701 positive at the Screening visit are allowed to enter the study on a dual-NRTI backbone that does not contain abacavir (see Section 5.6).

1.11.1.4. Study Procedures

Risks associated with study procedures include swelling, bleeding, bruising and infection from venipuncture required for blood sampling. These risks will be minimized using current standard of care techniques for venipuncture. Additionally, subjects will be required to have ECGs conducted periodically throughout the study; some discomfort and rash may occur where the ECG pads are removed.

1.11.1.5. Risk of Treatment Failure

This study employs an induction / maintenance approach to the treatment of HIV-1 infection. Following virologic suppression, subjects will be transitioned off of a 3 drug ART regimen to a 2 drug ART regimen. CAB and RPV have demonstrated antiviral activity in the Phase 2b studies LAI116482 (oral two drug treatment) and 200056 (through 48 weeks LA treatment). Viral loads will be closely monitored throughout the study.

Doses of the CAB LA and RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral formulations. Neither CAB LA nor RPV LA, at any dose, has been used in HIV-1 infected subjects. Plasma samples will be collected throughout the Maintenance Period for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response.

Due to administration error, it is possible that a subject could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly the development of resistance. HIV-1 RNA viral loads will be closely monitored throughout the injection period of the study.

Mitigation: HIV-1 RNA will be closely monitored throughout the study. Plasma samples will be collected throughout the Maintenance Phase for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response.

1.11.2. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochure. Please refer to Section 6: 'Summary of Data and Guidance for the Investigator'

Adverse Events of Special Interest:

Seizure:

Four cases of possible or definitive seizures have occurred in the CAB program cumulatively through 7 June 2016. Two of the cases occurred in HIV uninfected subjects with a prior history of seizure. Two cases occurred in HIV infected subjects, one case involved a subject in this study, 200056, and another case in the LAI116482 study, both cases displayed circumstantial and anecdotal evidence of illicit drug use which may have contributed to the event, and each case was determined by the Sponsor to not be reasonably likely related to CAB or RPV. Overall, there is insufficient evidence that CAB exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. However, seizure and seizure-like events will be closely monitored in clinical studies, including this study (200056). Any case of seizure or possible seizure must be reported to the Sponsor within 24 hours of notification, as detailed in Section 6.10.14.

1.11.3. Benefit Assessment

The antiviral activity of CAB has been well established through Phase IIa and Phase IIb studies and subjects receiving 30 mg of CAB + ABC/3TC are anticipated to benefit from attainment of virological suppression. RPV is an established antiviral agent in treatment naive patients, with long term durability (>96 weeks in Phase III and >240 weeks in Phase IIb). Subjects who achieve virologic suppression will be randomized to either a two-drug, two-class ART regimen containing CAB LA + RPV LA or to continue a suppressive oral regimen. Subjects randomized to an arm containing CAB LA + RPV LA will have infrequent, monthly or every other month dosing without the need to take concomitant daily oral therapy. The reduction in ART, and the discontinuation of NRTIs, may offer long term safety and tolerability benefits in these subjects.

Efficacy of the two-drug regimen, as oral agents, has been demonstrated through Week 96 of the ongoing LAI116482 study. Efficacy of the two-drug regimen, as LA agents, has been demonstrated through Week 48 of the ongoing 200056 study.

1.11.4. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with CAB, RPV and the study as a whole are justified by the anticipated benefits that may be afforded to treatment-naïve patients with HIV infection.

2. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To select an intramuscular dosing regimen of CAB LA plus RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg plus ABC/3TC orally once daily.	The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 based on intent to treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm. Proportion of subjects with protocol defined virologic failures over time
	Incidence and severity of AEs and laboratory abnormalities over time.
Secondary	
To evaluate the antiviral activity, tolerability, and safety of CAB 30 mg plus ABC/3TC orally once daily through the Induction and Maintenance Periods.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Absolute values and change from Baseline in plasma HIV-1 RNA. Absolute values and changes from Baseline in CD4+ cell counts. Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.
To evaluate the efficacy, tolerability, and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks, relative to CAB 30 mg plus ABC/3TC orally once daily, through Week 96 of the Maintenance Period.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Proportion of subjects with protocol defined virologic failures over time.
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death.

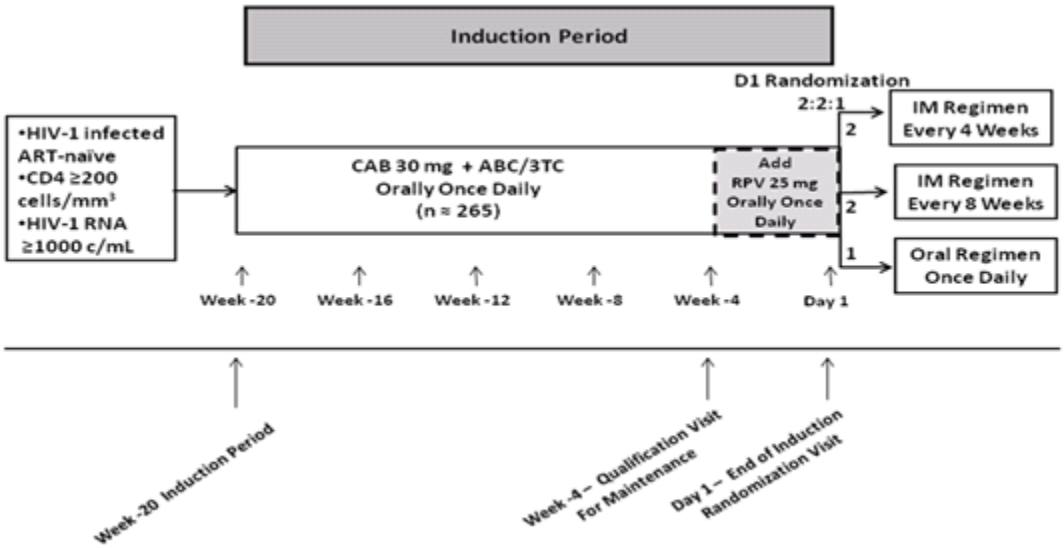
Objective	Endpoint
	Incidence and severity of AEs and laboratory abnormalities over time.
	Absolute values and changes in laboratory parameters over time.
To characterize CAB LA and RPV LA PK and to explore PK-PD relationships.	Plasma PK parameters for CAB LA and RPV LA (C_{trough} and concentrations post dose [~Cmax]) during the Maintenance Period. Plasma CAB and RPV trough concentrations will be used to determine when steady state is achieved for each CAB LA and RPV LA regimen. Relationship between plasma PK parameters and plasma HIV-1 RNA, CD4+ cell counts and/or occurrence of adverse events [AEs] through Week 48 of the Maintenance Period will be explored.
To assess the development of viral resistance in subjects experiencing protocol defined virologic failure.	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART.
To explore the effect of various demographic Baseline characteristics and adherence on virologic response of CAB and RPV over time.	Proportion of subjects with plasma HIV-1 RNA <50 c/mL over time.
To evaluate the treatment satisfaction for subjects on the long-acting injectable regimens with those on the oral regimen through Week 96 of the Maintenance Period.	Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time.
To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 32 of the Maintenance Period.	Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time.
To evaluate medication adherence over time.	Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.
Exploratory	
To evaluate the efficacy, tolerability, and safety of optimized IM dosing regimens CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Weeks 128 and 160 for subjects switching from the oral regimen therapy at the end of the Maintenace Period.	Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 128 and 160 (Missing, Switch or Discontinuation = Failure, Extension Switch population) Proportion of subjects with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 128 and 160

Objective	Endpoint
To evaluate the long term efficacy, tolerability, and safety of IM dosing regimens CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Week 160 for subjects who continued randomized IM dosing in the Extension Period.	using the FDA Snapshot algorithm (Extension Switch population) Proportion of subjects with protocol defined virologic failures over time Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Absolute values and changes in CD4+ cell counts over time Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.

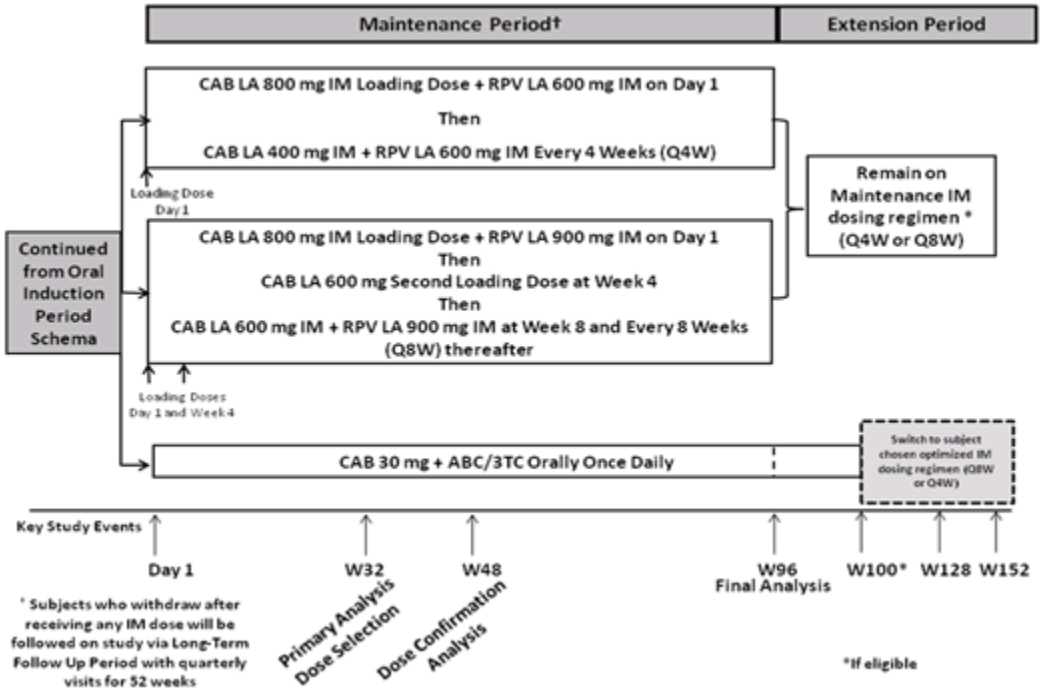
3. INVESTIGATIONAL PLAN

3.1. Study Design Schematic

Induction Period



Maintenance and Extension Period



3.2. Study Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Study 200056 is a Phase IIb, randomized, multicentre, parallel group, open-label, three-part study in HIV-1 infected ART-naive adults. The study will enroll approximately 265 subjects in order to randomize approximately 225 subjects at Day 1.

This study will consist of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn subjects only).

A subject is considered to have completed the study if they complete the Induction and Maintenance Period through Week 96.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2.1. Screening Period

Informed consent must be obtained prior to any study procedures, including any Screening assessment.

Subjects will participate in a screening period of up to 28 days. Subjects may be re-screened once. Subjects who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Subjects may be randomized as soon as all eligibility requirements have been met.

Subjects who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on a dual-NRTI backbone that does not contain abacavir. The selected dual-NRTI backbone may be supplied regionally by GlaxoSmithKline (GSK) or reimbursement will be provided.

3.2.2. Induction Period

Following the Screening Period, eligible subjects will be enrolled into the study and begin a 20 week Induction Period utilizing an oral regimen of CAB 30 mg once daily plus ABC/3TC 600/300 mg once daily.

Week -20 is considered the Baseline visit and is the first day on study treatment. Further weeks of treatment throughout the Induction Period will be counted up to Day 1 (Day 1 initiates the Maintenance Period).

Example: First day on study Week (-20)

Next visit Week (-16)

Next visit Week (-12), etc

Subjects will initiate treatment at Baseline (Week -20) and will be seen every 4 weeks for study treatment dispensing and safety and efficacy assessments (see Time and Events Section 6.1).

Unless subjects meet a study withdrawal criteria, their regimen will be modified at Week (-4) with the addition of RPV 25 mg once daily for the remainder of the Induction Period.

3.2.3. Eligibility for the Maintenance Period

All subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week (-4) are not eligible to enter the Maintenance Period and will not be allowed a repeat to determine eligibility.

Result of HIV-1 RNA at Week (-4)	Action
<50 c/mL	Begin Maintenance Period
≥50 c/mL but <400 c/mL	Single repeat allowed only after consultation and approval from medical monitor
Single repeat <50 c/mL	Begin Maintenance Period
Single repeat ≥50 c/mL	Cannot begin Maintenance Period and must be withdrawn from study; Complete withdrawal visit instead of Day 1.
≥400 c/mL	Cannot begin Maintenance Period and must be withdrawn from study; Complete withdrawal visit instead of Day 1

Should a subject be allowed a repeat, results of this repeat must be available prior to Day 1, therefore the time needed for scheduling the visit, lab draws and lab analysis should be considered.

The medical monitor may advise the site to withdraw a subject from the study prior to Week (-4) to avoid initiating RPV in a subject who is unlikely to be eligible for the Maintenance Period.

In addition to the viral load criteria above, if in the opinion of the Investigator, a subject experiences a significant safety event while taking either CAB or RPV, Maintenance eligibility will be determined ONLY in consultation with the medical monitor. **Any rash that is possibly related to study drug, and is present between Week (-4) and Day 1, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA (See Section 6.10.6.15).**

Subjects ineligible for the Maintenance Period will be withdrawn.

If the subject is ineligible for the Maintenance Period, samples will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Maintenance Period.

3.2.4. Maintenance Period

At Day 1, the Maintenance Period begins. Eligible subjects will be randomized 2:2:1 to receive an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 96 weeks, an IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks for 96 weeks, or to continue on the oral Induction Period regimen of CAB 30 mg + ABC/3TC

once daily for 96 weeks (or 100 weeks if continuing on to the Extension Period). Subject randomization will be stratified by subjects' HIV-1 RNA prior to Week (-8) (<50 c/mL, yes or no).

On the first day of the Maintenance Period (Day 1), subjects will receive their last dose of the Induction regimen (CAB+ABC/3TC+RPV) in the clinic and initiate either IM injections or be dispensed the oral regimen depending on the randomization arm. Add-on RPV treatment will be discontinued for all subjects after Day 1.

Dosing for each arm is as follows (all injections are single injections per drug unless otherwise noted):

- IM injections every 8 weeks (Q8W)

  Day 1 only – CAB LA 800 mg (loading dose delivered as two 400 mg IM injections) + RPV LA 900 mg IM

  Week 4 only - CAB LA 600 mg IM (second loading dose, no RPV)

  Week 8 - CAB LA 600 mg IM + RPV LA 900 mg IM every 8 weeks for 96 weeks

- IM injections every 4 weeks (Q4W)

  Day 1 only - CAB LA 800 mg (loading dose delivered as two 400 mg IM injections) + RPV LA 600 mg IM

  Week 4 - CAB LA 400 mg IM + RPV LA 600 mg IM every 4 weeks for 96 weeks

- Oral Control Arm

  CAB 30 mg + ABC/3TC once daily for 96 weeks (or 100 weeks if continuing on to the Extension period)

It is important to note that keeping to the subject's visit schedule is a very important component to the study. IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). A (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred.

Visits for subjects on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit.

All subjects are seen approximately every 4 weeks for safety, efficacy and PK assessments through Week 32. After Week 32, subjects will continue to be seen as per the Time and Events Schedule (see Section 6) for dosing, safety, efficacy and PK assessments through Week 96 (or Week 100 for the oral arm if subject is continuing on to the Extension Period).

Some visits that are not aligned with dosing will be conducted by telephone interview. This allows for safety assessments to be conducted at all visits, but limits clinic visits for non-dosing visits. Telephone safety assessments will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including injection site reactions or oral compliance issues. Telephone visits will be clearly noted in the Time and Events Schedule.

See the Time and Events Schedule Section 6.2 and Section 6.3 for more information. See Section 3.2.5.3 for additional information regarding special requirements from Week 96 to Week 104 for subjects on the oral arm entering the Extension Period.

If one of the IM dosing regimens (Q8W or Q4W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued dosing regimen may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

3.2.5. Extension Period

Both IM dosing regimens (Q8W and Q4W) will continue evaluation in the Extension period. Subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option of continuing study participation by switching to an optimized IM dosing regimen of their choice (either Q8W or Q4W).

3.2.5.1. Entering from the CAB LA + RPV LA Arm

All subjects who successfully complete 96 weeks of CAB LA + RPV LA treatment in the Maintenance Period will continue with their current IM dosing regimen of CAB LA and RPV LA in the Extension Period until:

- study treatment is locally approved and commercially available,
- the subject no longer derives clinical benefit,
- the subject meets a protocol-defined reason for discontinuation
- the development of either CAB LA or RPV LA is terminated.

Subjects will remain on their current regimen after Week 96 and will continue to receive their Maintenance Period IM dosing regimen for the remainder of study participation. Safety and efficacy assessments will be conducted every 16 weeks. Dosing visits will occur according to the selected dosing regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.

3.2.5.2. Eligibility for the Extension Period for Subjects Entering From the CAB 30 mg + ABC/3TC Arm

All subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit are eligible to enter the Extension Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1

RNA ≥400 c/mL at Week 96 are not eligible to enter the Extension Period and will not be allowed a repeat to determine eligibility.

Result of HIV-1 RNA at Week 96	Action
<50 c/mL	Begin Extension Period
≥50 c/mL but <400 c/mL	Single repeat allowed only after consultation and approval from medical monitor
Single repeat <50 c/mL	Begin Extension Period
Single repeat ≥50 c/mL	Cannot begin Extension Period and must be withdrawn from study; Complete withdrawal visit.
≥400 c/mL	Cannot begin Extension Period and must be withdrawn from study; Complete withdrawal visit.

Should a subject be allowed a repeat, results of this repeat must be available prior to next visit, therefore the time needed for scheduling the visit, lab draws and lab analysis should be considered.

In addition to the viral load criteria above, if in the opinion of the Investigator, a subject experiences a significant safety event while taking either CAB or RPV, Extension eligibility will be determined ONLY in consultation with the medical monitor.

Subjects ineligible for the Extension Period will be withdrawn.

If the subject is ineligible for the Extension Period, samples will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

3.2.5.3. Entering from the CAB 30 mg + ABC/3TC Arm

All subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option to continue study participation by switching to the optimized IM dosing regimen of their choice (either Q8W or Q4W) of CAB LA + RPV LA in the Extension Period. Subjects not choosing to switch to an optimized long acting regimen will complete their study participation at Week 96.

Subjects who choose to continue on to the Extension Period will be assessed for eligibility to begin their selected CAB LA + RPV LA regimen as described in Section

3.2.5.2. Subjects will continue on their oral Maintenance regimen (CAB 30 mg + ABC/3TC) until Week 100 while eligibility is being confirmed. RPV will not be added to their Maintenance regimen prior to the switch to optimized IM dosing. Subjects were given RPV during the last 4 weeks of the Induction Period to evaluate safety and tolerability before being randomized to continue in the Maintenance Period and thus further evaluation is not necessary.

In order to qualify to receive CAB LA + RPV LA injections at Week 100, the HIV-1 RNA results from the Week 96 visit must be undetectable (<50 c/mL; a single repeat HIV-1 RNA test may be allowed prior to Week 100 following consultation with the Medical Monitor).

If the Optimized Q4W IM Dosing Regimen is selected by the Subject:

At visit Week 100, participants will return to the clinic, take the last dose of their oral regimen (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104 and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104, but not later than Week 104, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 injection, the interval between injection visits should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds, or is projected to exceed, 5 weeks from the previous injection.

If the Optimized Q8W IM Dosing Regimen is selected by the Subject:

At visit Week 100, subjects will return to the clinic, take the last dose of their oral (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second loading injections will be administered at Week 104 (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 8 weeks thereafter. The dosing window for the second injection allows administration between Week 103 and Week 104, but preferably not later than Week 104. Starting at the Week 112 injection, the interval between injection visits should be limited to a maximum of 9 weeks. If the length of time between injections exceeds, or is projected to exceed 9 weeks, the Medical Monitor must be contacted to discuss individual subject case management. After Week 112, a dosing window (±7 days) for injections is allowed, but not preferred.

Subjects will continue study treatment until:

- study treatment is locally approved and commercially available,
- the subject no longer derives clinical benefit,
- the subject meets a protocol-defined reason for discontinuation

- the development of either CAB LA or RPV LA is terminated.

Safety and efficacy assessments will be conducted as per the Time and Events schedule (Section 6.5 and Section 6.6 for more information). Dosing will occur according to the selected regimen.

Subjects not eligible to enter the Extension Period will end their study participation. Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

If one of the optimized IM dosing regimens (Q8W or Q4W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who selected a discontinued optimized IM dosing regimen may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

3.2.6. Long-term Follow-Up Period – IM Regimens only

Any subject who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive Highly Active Antiretroviral Treatment (HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. This period is considered study participation and subjects will be followed on study during this time.

In the Long-Term Follow-Up Period, subjects will receive oral HAART and will be followed for 52 weeks after the last dose of CAB LA and/or RPV LA. **Investigators must discuss the choice of HAART regimen and timing of initiation with the medical monitor before initiating.** The 52 weeks follow up period will begin the day of the last CAB LA and/or RPV LA dose. These subjects will not complete a Withdrawal visit, but will instead move directly into the Long-Term Follow Up Period as per the Time and Events Schedule (see Section 6.7).

Subjects will be assessed with clinic visits at months 1, 3, 6, 9 and 12. Female subjects of child bearing potential must continue to use adequate contraception methods (see Study Procedures Manual for list of accepted forms of contraception) for the entire year of follow up.

In order to assure that subjects have access to HAART during the Long-Term Follow-Up Period, GSK may supply HAART regionally or reimbursement will be provided during this period.

3.2.7. Follow Up Visit

A Follow up visit may be conducted approximately 4 weeks after the last dose of IP and is required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. The assessments performed should reflect what is considered medically necessary

to assess the event(s). The Follow-up visit may be conducted via telephone if the subject has no ongoing adverse events or other issues that would require a clinic visit.

This visit is not required for subjects in the Long-Term Follow Up Period.

3.2.8. Independent Data Monitoring Committee

An IDMC will evaluate the efficacy, tolerability, and safety of CAB and RPV before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. This IDMC review may be conducted after approximately 45 subjects have reached Week 8 of the Maintenance Period, depending on IDMC agreement. The intent of this analysis is to identify any early safety or tolerability signals from the long acting regimen. In addition, futility guidance (e.g., a Bayesian posterior probability approach when 50% of subjects have completed Week 24 of the Maintenance Period) is included to monitor the performance of all treatment arms in order to prevent subjects from continuing on a dosing regimen if existing data indicates that subjects are at unacceptable risk of inadequate maintenance of virologic suppression.

If one of the IM dosing regimens (Q8W or Q4W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued dosing regimen, or selected a discontinued optimized IM dosing regimen, may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

As subjects enter the Maintenance Period of the study, if the number of protocol defined virologic failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. Similar thresholds will be used by the IDMC to monitor the number of protocol defined virologic failures for subjects switching from oral CAB 30 mg + ABC/3TC to an optimized IM dosing regimen during the Extension Period. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

3.2.9. Primary Analysis

The primary analysis will be conducted when all subjects have completed their Maintenance Period Week 32 visit. This analysis will characterize the safety, tolerability and durability of antiviral response from both the Induction Period and the Maintenance Period. Planned analyses will also be conducted at Week 48, Week 96, Week 128 and Week 160. Follow-up analyses of data collected after subjects have entered into the Extension Period may be conducted to more fully characterize the long-term safety and efficacy profile of CAB and RPV.

3.3. Discussion of Design

Study 200056 is a Phase IIb assessment of a regimen consisting of the long-acting injectable forms of CAB and RPV to maintain virologic suppression in previously untreated HIV-infected subjects without evidence of transmitted resistance who achieve virologic suppression on CAB plus ABC/3TC. The ongoing study LAI116482 provides support for this unique approach of a two-class, two-drug regimen. Results from planned analyses of LAI116482 support the choice of 30 mg CAB for use in the Induction Period of this study. Exposure and efficacy data from LAI116482 as well as exposure data from the repeat dose studies with CAB LA and RPV LA defined the target doses and exposures for CAB LA and RPV LA during the Maintenance Period. Systemic exposure of RPV obtained with RPV LA is aimed to be comparable to that obtained with RPV, for which the antiviral activity and safety has been well established through Phase III studies.

Long acting CAB has been investigated in 136 healthy subjects to date as both SC and IM injections. This study will be the first evaluation of CAB LA or RPV LA in HIV-infected subjects. The results to date support CAB LA and RPV LA for continued clinical development. Injection site reactions (ISR) of both agents have been generally mild, self-limited, and well-tolerated in single and multiple dose studies.

The results of LAI116482 support the use of oral CAB plus NRTIs as a reference regimen to the investigational two-drug long-acting regimen. At the primary endpoint of Week 48, the response rates (HIV-1 RNA <50 c/mL; ITT, MSDF, Table 1) for the three doses of CAB in the LAI116482 study were 80%, 80% and 87% for the 10 mg, 30 mg, and 60 mg arms, respectively. These rates compare favorably to the control regimen of EFV plus NRTIs in this study where 71% of subjects achieved HIV-1 RNA <50 c/mL at Week 48.

These data indicate continued viral suppression after 24 weeks of the two drug CAB and RPV regimen.

The ITT-Maintenance Exposed (ITT-ME) Population consists of all randomized subjects who received at least one dose of investigational product during the Maintenance Phase of the study. Of the subjects who entered the Maintenance Phase of the study, the majority remained suppressed through Week 48 (24 weeks of two drug therapy) (Table 3).

Table 3 LAI116482 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-ME Population)

Visit	GSK744 10 mg N=52 n (%)	GSK744 30 mg N=53 n (%)	GSK744 60 mg N=55 n (%)	GSK744 Subtotal N=160 n (%)	EFV 600 mg N=47 n (%)
Week 16 - Induction	50 (96)	49 (92)	52 (95)	151 (94)	43 (91)
Week 24 - Induction	50 (96)	50 (94)	53 (96)	153 (96)	45 (96)
Week 48 - Maintenance	48 (92)	48 (91)	53 (96)	149 (93)	44 (94)

The background NRTIs (ABC/3TC) are accepted agents for initiation of antiretroviral therapy in treatment guidelines [EACS, 2012; DHHS, 2013] and as such are considered appropriate for this trial. RPV is approved as Edurant for use in combination ART at an

oral dose of 25 mg, once daily with a meal in treatment naive patients [Edurant Product Information, 2015].

This trial is designed to evaluate two distinct periods. First, to evaluate the ability of CAB + background NRTIs to induce virologic suppression during the Induction Period. Second, during the Maintenance Period, two different dosing strategies of a long-acting, two-drug, two-class regimen will be evaluated on their ability to maintain virologic efficacy for 96 weeks compared to a control regimen of oral CAB + ABC/3TC.

The primary endpoint, proportion of subjects with plasma HIV-1 RNA < 50 c/mL, is a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2002]. The primary endpoint for this study is proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 32 and will be used to select an IM dosing regimen (Q8W or Q4W). Week 32 has been selected to allow a comparable evaluation among the dosing regimens. Q8W begins dosing at Week 8, following a loading dose at Day 1 and Week 4. Therefore, choosing Week 32 as an endpoint allows for a 24 week evaluation of the Q8W arm at steady state.

The Week 48 analysis will permit an evaluation of the ability of the investigational two-drug long-acting combinations to maintain virologic suppression over time, and will serve as the dose confirmation of the dosing regimen selected at Week 32. Longer term durability of virologic suppression for these long-acting two-drug regimens will also be evaluated through a formal Week 96 analysis.

The Extension Period will allow participants on the oral Maintenance Period regimen who successfully complete Week 96 with an HIV-1 RNA viral load <50 c/mL the opportunity to choose an optimized IM dosing regimen (Q8W or Q4W). This will permit an evaluation of the ability of the optimized investigational two-drug long acting combinations (see Section 5.1.6) to maintain virologic suppression over time. This period will also allow participants currently on a IM Maintenance Period regimen who successfully complete Week 96 with an HIV-1 RNA viral load <50 c/mL the ability to continue to receive their current IM dosing regimen and to generate additional long-term safety and efficacy data for randomized IM dosing regimens.

A planned Week 128 analysis will primarly evaluate the efficacy, tolerability, and safety of the optimized IM dosing regimens through 28 weeks of optimized IM treatment in subjects switching from oral Maintenance therapy. Long term durability of virologic suppression of the randomized long-acting two-drug regimens through Week 128 may also be evaluated.

A Week 160 analysis will permit an evaluation of the ability of the randomized and optimized investigational two-drug long-acting combinations to showcase long-term durability of virologic suppression. Additional long-term safety and efficacy data for all IM dosing regimens will be generated.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Sufficient subjects will be screened (approximately 350) in order to ensure that a total of approximately 265 subjects are enrolled at the beginning of the Induction Period and to ensure approximately 225 subjects are randomized into the Maintenance Period. Subjects will be enrolled from multiple sites which may include sites in the US, Canada, France, Germany, and/or Spain.

4.2. Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

In general, subjects screened for this study must:

- be able to understand and comply with protocol requirements, instructions, and restrictions,
- be likely to complete the study as planned,
- understand the long term commitment to the study,
- be considered appropriate candidates for participation in an investigative clinical trial with oral and intramuscularly injectable medications (e.g., no active substance abuse, acute major organ disease).

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational regimen or other study treatment that may impact subject eligibility is provided in the current Investigator's Brochure (IB) for CAB and RPV and in the current prescribing information for ABC/3TC.

A single repeat of a procedure / lab parameter is allowed to determine eligibility (unless otherwise specified).

Subjects are allowed to re-screen for this study one time. This will require a new subject number.

The following are study specific eligibility criteria unless stated otherwise**. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study subjects, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP). All subjects must be considered appropriate candidates for initiation of antiretroviral therapy in accordance with local treatment guidelines.**

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility.

Subjects eligible for enrollment in the study **must** meet all of the following criteria:

1. HIV-1 infected subjects ≥18 years of age.
2. A female subject is eligible to enter and participate in the study if she:
   a. is of non-child-bearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or
   b. is of child-bearing potential with a negative pregnancy test at both Screening and first day of the Induction Period and agrees to use one of the following methods of contraception to avoid pregnancy 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all oral study medications and for at least 52 weeks after discontinuation of CAB LA and RPV LA:
      - Complete abstinence from intercourse (where this is the subject's preferred and usual lifestyle).
      - Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide).
      - Approved hormonal contraception (see the SPM for a listing of examples of approved hormonal contraception).
      - Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion, see the study procedures manual [SPM] for specifics).
      - Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject.
      - Any other method with published data showing that the lowest expected failure rate is <1% per year.
      - Any contraception method must be used consistently and in accordance with the approved product label.

   ALL subjects participating in the study must be counseled on safer sexual practices including the use of effective barrier methods to minimize risk of HIV transmission.

- HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 c/mL.
- CD4+ cell count ≥200 cells/mm3 (or higher as local guidelines dictate).
- ART-naive defined as having no more than 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection. Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor will be exclusionary.

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must **not** be enrolled in the study:

Exclusionary Medical Conditions

1. Women who are breastfeeding.
2. Any evidence at screening of an active Centers for Disease and Prevention Control (CDC) Category C disease [Centers for Disease Control and Prevention (CDC), 1993], except cutaneous Kaposi's sarcoma not requiring systemic therapy.
3. Subjects with known moderate to severe hepatic impairment.
4. Any pre-existing physical or mental condition (including substance abuse disorder) which, in the opinion of the Investigator, may interfere with the subject's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the subject.
5. Subject who, in the investigator's judgment, poses a significant suicide risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk.
6. The subject has a tattoo or other dermatological condition overlying the gluteus region which may interfere with interpretation of injection site reactions.
7. History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (Hepatitis B Virus surface Antigen [HBsAg] positive).
8. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy must be excluded.
9. History of liver cirrhosis with or without hepatitis viral co-infection.
10. Ongoing or clinically relevant pancreatitis.
11. History of the following cardiac diseases: myocardial infarction, congestive heart failure, documented hypertrophic cardiomyopathy, sustained ventricular tachycardia.
12. Personal or known family history of prolonged QT syndrome.
13. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the drug or render the subject unable to receive study medication.
14. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin is used during PK sampling, subjects with a history of sensitivity to heparin or heparin-induced thrombocytopenia must not be enrolled.

15. Current or anticipated need for chronic anti-coagulation.

Exclusionary Laboratory Values or Clinical Assessments at Screening (a single repeat to determine eligibility is allowed)

16. Any evidence of primary resistance based on the presence of any major resistance-associated mutation (International AIDS Society [IAS]-USA, 2013) in the Screening result or, if known, any historical resistance test result. Note: re-tests of Screening genotypes are allowed only at the discretion of the study virologist.
17. Any verified Grade 4 laboratory abnormality.
18. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound.
19. Subject has estimated creatinine clearance <50 mL/min via Cockcroft-Gault [Cockcroft, 1976] method.
20. Alanine aminotransferase (ALT) ≥5 times ULN. Subjects with ALT > 2xULN but <5xULN may participate in the study, if in the opinion of the Investigator and GSK medical monitor the lab abnormality will not interfere with the study procedures or compromise subject safety.
21. Alanine aminotransferase (ALT) ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
22. Any clinically significant finding on screening or Baseline electrocardiograph (ECG), specifically:

	Males	Females
Heart rate*	<45 and >100 bpm	<50 and >100 bpm
QRS duration	>120 msec	
QTc interval (B or F)	>450 msec	

*A heart rate from 100 to 110 bpm can be rechecked within 30 minutes to verify eligibility.

- Non-sustained (≥3 consecutive beats) or sustained ventricular tachycardia.
- Sinus pauses >2.5 seconds.
- 2nd degree (Type II) or higher atrioventricular (AV) block.
- Evidence of WPW (Wolff- Parkinson-White) syndrome (ventricular preexcitation).
- Pathologic Q waves (defined as Q wave > 40msec OR depth >0.4 mV.
- Any significant arrhythmia (either on ECG or by history) which, in the opinion of the Investigator and GSK medical monitor, will interfere with the safety for the individual subject.

23. Subjects who are HLA-B*5701 positive and unable to use an alternative NRTI backbone (subjects who are HLA-B*5701 positive may be enrolled if they use an alternative NRTI backbone that does not contain abacavir).

Exclusionary Treatments prior to Screening or First Day of Induction Period

24. Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP.
25. Treatment with any of the following agents within 28 days of Screening:
    - radiation therapy
    - cytotoxic chemotherapeutic agents
    - tuberculosis therapy
    - Immunomodulators that alter immune responses (such as systemic corticosteroids, interleukins, or interferons) Note: Subjects using short-term (<10 day) steroid tapers, topical, inhaled and intranasal corticosteroids are eligible for enrollment.
26. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening.
27. Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 within 28 days of the first dose of IP.

Notwithstanding these minimum inclusion and exclusion criteria, investigators must also follow country specific guidelines where they exist when making decisions about subjects who are eligible for study participation.

4.4. Additional Eligibility Criteria

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the current IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the IP and the dual NRTI background drugs being used in this study.

4.5. Withdrawal Criteria

Subjects permanently discontinuing study treatments prior to Week 96 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects permanently discontinuing participation from the Extension and Long-Term Follow-Up Period prior to commercially available drug supply are considered to be withdrawn from the study treatments and also from the study.

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at their discretion, discontinue the subject from participating in this study at any time. Subjects who are withdrawn from the study will not be replaced.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the

study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the electronic case report form (eCRF).

Subjects are not obligated to state the reason for withdrawal but the Investigator must make every attempt to elucidate a reason. The efforts must be documented in the source including efforts to locate a subject that has been deemed lost to follow up. The reasons for withdrawal, or failure to provide a reason, must be documented in the eCRF.

The investigator must make every effort to perform a Withdrawal visit as well as a Follow-Up visit (as needed) as per the Time and Events Table (see Section 6). Follow-up for AEs and SAEs must occur as specified in Section 6.10.12.

Subjects with an HIV-1 RNA > 200 c/mL at the time of Withdrawal will have samples sent to a central laboratory for resistance testing and results provided to the Investigator once available.

All subjects who discontinue prematurely from the study, irrespective of arm, will be asked for additional information to establish the reason for withdrawal.

Reasons for study withdrawal may include:

- Adverse event/Serious adverse event
- Protocol deviation
- Intolerability of injections
- Subject lost to follow-up
- Subject withdrew consent
- Investigator discretion
- Subject or investigator non-compliance
- Termination of the study by the Sponsor
- At the request of the subject, Investigator, or GSK
- The subject requires concurrent prohibited medications during the course of the study. If, in the opinion of the Investigator and the study medical monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject, then the subject may remain in the study.

Subjects must be withdrawn from the study for any of the following reasons:

- Subjects who are not eligible to continue into the Maintenance Period as per Section 3.2.3.
- Subjects who do not wish to continue on the remaining dosing regimen if one dosing regimen is discontinued further to an IDMC decision (see Section 3.2.8).
- Subjects who are not eligible, or do not wish to continue on to the Extension Period (see Section 3.2.5.3).
- Subjects who cannot or do not wish to continue on to the Long-Term Follow Up Period (see Section 3.2.6).
- Confirmed virologic failure as described in Section 4.6.
- Pregnancy (intrauterine).
- Subject requires a switch of background NRTI therapy (except as allowed in Section 5.6).
- Subject requires substitution or dose reduction of CAB or RPV.
- Grade 4 AE or toxicity in the absence of compelling evidence that the AE is not causally related to the IP (See Section 6.10.6.4).
- Liver toxicity where Stopping Criteria as described in Section 6.10.3 are met and no compelling alternative cause is identified.
- Renal toxicity as specified in Section 6.10.6.9 and Section 6.10.6.10 is met and no compelling alternate cause is identified.
- Subject has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement as described in Section 6.10.6.15.
- The following QT criteria:
  - Corrected QT interval (QTc) >500 msec
  - Uncorrected QT >600 msec

  These criteria must be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study.

  For subjects with underlying Bundle Branch Block:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450-480 msec	≥530 msec

Efficacy data for subjects withdrawing from the study will be considered evaluable up to the point at which they are withdrawn using the same criteria for evaluability as for subjects who complete the study.

Safety data for all subjects who receive any amount of study drug, including subjects who withdraw from the study, will be included in evaluations of safety.

4.5.1. Subjects Receiving CAB LA and / or RPV LA

Subjects who have received at least one dose of CAB LA or RPV LA and choose to withdraw or are required to withdraw, will be asked to participate in the Long-Term Follow Up Period of the study (See Section 3.2.6). The investigator must make every effort to conduct visits as per the Time and Events Table (see Section 6.7).

The Investigator must discuss choice of follow-up HAART regimen and timing of initiation with the medical monitor prior to initiating the new regimen with the subject.

4.6. Virologic Failure

Following study entry, no changes, or intensification of ART will be permitted prior to protocol-defined virologic failure, with the exception of the planned addition of RPV at Week (-4), the change to the Maintenance Period regimen, and one allowed alternative approved NRTI change for management of drug toxicity.

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Baseline plasma HIV-1 RNA is the assessment completed on the first day of the Induction Period.

The definition of protocol defined virologic failure does not apply to subjects in the Long-Term Follow-Up Period. These subjects will be followed for the emergence of potential virologic resistance only. If the HIV-1 RNA > 200 c/mL, a confirmation sample must be obtained. If the repeat HIV-1 RNA is > 200 c/mL samples will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

4.6.1. Definition of Virologic Failure

For the purposes of clinical management in this study, virologic failure is defined as **any** of the following:

- Non-response as indicated by a less than a 1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA after 4 weeks of starting the Induction Period, which is subsequently confirmed, unless the plasma HIV-1 RNA is < 400 c/mL.
- Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥ 200 c/mL after prior suppression to < 200 c/mL.
- Rebound as indicated by two consecutive plasma HIV-1 RNA that are > 0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the lowest HIV-1 RNA value is ≥ 200 c/mL.

4.6.2. Managing Virologic Failure

Inadequate adherence is a common cause for virologic failure, and should be explored as a first step in the management of study subjects (e.g., at the first indication of inadequate virologic response or rebound).

4.6.2.1. Suspected Virologic Failure

Upon notification that a subject's HIV-1 RNA plasma level meets any of the definitions of virologic failure, the Investigator should confirm the definition is met by initiating a repeat of the HIV-1 RNA assessment.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the subject should receive full dose of all IP.
- If therapy is interrupted* due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of all IP.
- The subject should have received full dose of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

*Note: treatment interruption guidelines above may not apply for subjects on CAB LA + RPV LA treatment. The study team should be contacted to discuss any treatment interruptions for subjects meeting the definition of virologic failure.

In addition, the Investigator should query the subject regarding intercurrent illness, recent immunization, or interruption of therapy.

Sites should contact the study medical monitor to discuss individual subjects, whenever necessary.

4.6.2.2. Confirmed Virologic Failure

Subjects who confirm virologic failure must be discontinued from the study. However, subjects who have received at least one dose of CAB LA or RPV LA prior to confirming virologic failure will remain in the study on oral HAART in the Long-Term Follow Up Period (see Section 3.2.6).

A plasma sample from the suspected virologic failure visit as well as the first day of the Induction Period (Baseline) will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available. A plasma sample from the confirmation visit will be obtained for storage. This sample may be used for possible

future analyses, e.g. for genotypic and phenotypic analyses of subjects who experience virologic failure.

4.7. Screening Failures

Subjects who do not meet ALL Inclusion, Exclusion and any other eligibility criteria will be considered Screen Failures. Basic study data will be collected for all screened subjects including the reason for screen failure. Subjects are allowed to rescreen once but the subject will be assigned a new subject number. Subjects who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

In this study, investigational product (IP) refers to CAB, CAB LA, RPV and RPV LA. These will be supplied by GlaxoSmithKline and Janssen Pharmaceuticals, respectively. Epzicom / Kivexa will also be considered IP from Day 1 of the Maintenance Period and will be provided by GSK.

Other antiretrovirals administered in the study as dual background NRTIs (e.g. for subjects who are HLA-B*5701 positive or switch due to toxicity) are not considered IP. These may be supplied regionally by GSK or reimbursement will be provided.

The contents of the labels will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product and background NRTIs must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product and background NRTIs will be limited to the investigator and authorised site staff. Investigational product and background NRTIs must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

5.1.1. Cabotegravir (GSK1265744) – Tablet (CAB)

CAB is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an

induction seal. CAB tablets will be packaged in bottles of 30 tablets. Subjects must keep all IP in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes. CAB tablets are to be stored up to 30°C and protected from moisture.

5.1.2. Rilpivirine - Tablet (RPV)

RPV [Edurant Product Information, 2015] is provided by Janssen Research & Development, a division of Janssen Pharmaceuticals as 25 mg tablets that are off-white, round, biconvex, film-coated and debossed on one side with "TMC" and the other side with "25". RPV is manufactured by Janssen -Cilag S.p.A, Latina, Italy. RPV will be provided as globally marketed product, including US and the European Union, and overlabeled, packaged in bottles of 30 tablets. RPV tablets are to be stored at 25°C (excursions permitted to 15°-30°C [59°-86°F]) and protected from light.

5.1.3. Epzicom / Kivexa

ABC/3TC [Epzicom Product Information, 2012] is manufactured by GlaxoSmithKline and is supplied as the ABC/3TC fixed dose combination (FDC) oral tablet, which contains 600 mg of ABC (as abacavir sulfate) and 300 mg of 3TC. The tablets are orange, film-coated, modified capsule-shaped and debossed with GS FC2 on one side with no markings on the reverse side. ABC/3TC is packaged in bottles of 30 tablets. ABC/3TC will be supplied by GSK as commercial product. ABC/3TC tablets are to be stored at 25°C (excursions permitted to 15°-30°C [59°-86°F]).

5.1.4. Cabotegravir (GSK1265744) – Injectable Suspension (CAB LA)

CAB LA is manufactured by GlaxoSmithKline and is a sterile white to slightly colored suspension containing 200 mg/mL of CAB as free acid for administration by intramuscular (IM) injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and aluminium seal. Each vial is for single use containing a withdrawable volume of 2.0 mL, and does not require dilution prior to administration. CAB LA injectable suspension is to be stored at up to 30°C, do not freeze.

CAB LA is composed of cabotegravir free acid, polysorbate 20, polyethylene glycol 3350, mannitol, and water for injection.

5.1.5. Rilpivirine – Injectable Suspension (RPV LA)

RPV LA, also named JNJ-16150108-AAA 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, a division of Janssen Pharmaceuticals as a sterile white suspension containing 300 mg/mL of RPV as free base for administration by intramuscular (IM) injection. The product is packaged in a single use 4 mL USP Type I glass vial with a 13 mm grey stopper and aluminium seal. Each vial is for single use containing a nominal fill of 2.0 mL, and does not require dilution prior to administration but requires refrigeration. RPV LA injectable suspension is to be stored 2-8°C, do not freeze, protected from light and kept in the outer package.

RPV LA is composed of RPV free base, poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, glucose monohydrate, sodium hydroxide, water for injection.

5.1.6. Dosage and Administration

Following is a table of dosing and administration for all treatment arms:

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections (No RPV LA)
Week 8 to Week 88 (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 600 mg given as 1 X 2 mL IM injection

Week 4 to Week 92 (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
CAB 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
If continuing to Extension Period:	
Week 96 to Week 100 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Extension Period (Week 96 +)	
If subject was randomized to the Q8W regimen during the Maintenance Period:	
Week 96 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
If switching from Oral Arm and the Optimized Q8W regimen is selected by subject:	
Week 100 – 1st loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose (2 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 112 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection

If Subject was Randomized to the Q4W regimen during the Maintenance Period:	
Week 96 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm and the Optimized Q4W regimen is selected by subject:	
Week 100 – 1st loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose (2 injections once)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 108 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection

*Or through Week 100 if eligible to enter the Extension Period.
+until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of CAB or RPV is terminated

5.1.7. Dosing Considerations for CAB LA + RPV LA

Vials of CAB LA and RPV LA are each supplied as a suspension and need no further dilution or reconstitution. However, sites should gently invert the vials a few times to re-suspend sediments and allow bubbles to subside, and then use a syringe to withdraw the required volume of suspension for IM injection. Since RPV LA requires refrigeration sites should allow the vial to come to approximately room temperature prior to injecting.

All injections must be given intramuscularly in the gluteus medius. Sites may use their discretion as to where in the gluteus muscle each injection is given according to individual subject circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction. The time and location of injection will be captured in the eCRF.

IM injections should be administered at a 90 degree angle into the gluteus medius muscle using a 1.5” 25 gauge needle for CAB LA and a 1.5” 21 gauge needle for RPV LA in most subjects. The needle should be long enough to reach the muscle mass and prevent study drug from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Variable needle lengths may need to be used to accommodate individual body type. For example, longer needle lengths may be required for subjects with higher body mass indexes (BMIs, example > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. BMI and needle length used will be collected in the eCRF.

On Day 1, subject should be dosed with the IM regimen within 2 hours of taking the last Induction regimen dose where possible. The same should apply to subjects switching from the oral regimen to an IM regimen at Week 100.

Should the subject have intolerance to the single 3 mL injection, the injection may be administered as 2 separate 1.5 mL injections with the assent of the medical monitor. If the injection is split, this will be noted in the eCRF and the intolerance captured as an AE.

Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the subject stay onsite for up to 2 hours post dose for safety monitoring and notifying the medical monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV concentrations.

Additional dosing instructions and considerations can be found in the SPM.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule.

Following completion of the Induction Period, subjects eligible to enter the Maintenance Period will be randomized 2:2:1 to Q8W or Q4W of CAB LA + RPV LA or to the oral control arm (CAB 30 mg + ABC/3TC). Randomization will be stratified by HIV-1 RNA result before Week (-8) (<50 c/mL yes or no). Randomization will be conducted via a central randomization procedure. The central randomization schedule, including stratification, will be generated using the GSK validated randomization software RANDALL. Study site personnel will be required to call the central randomization service for assignment of a unique identifier (designating the subject's randomization code and treatment sequence assignment) for each subject participating in the study. A unique treatment number will be assigned for each subject participating in the study.

5.3. Blinding

This study is not blinded.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Treatment compliance will be evaluated using pill counts of unused IP (CAB 30 mg and RPV 25 mg tablets). This assessment will be conducted each time the subject receives a

new (refill) supply of oral study medication. Additionally, the date and time of each injection of CAB LA and RPV LA will be noted. These data will be recorded in the subject's eCRF.

Treatment compliance will not be assessed during the Long-Term Follow-Up Period.

Due to the long acting nature of the CAB and RPV, it will be imperative that the subject is compliant with dosing instructions. Subject awareness and knowledge of these dosing instructions will be assessed by reviewing the answers to the HIVMQ as discussed in Section 6.14.

Investigators must have plans in place for adherence counselling. In addition, Investigators must have plans in place to perform visit reminders and to verify the subject's contact information at each visit.

5.6. Protocol Permitted Substitutions

Subjects who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on an approved dual-NRTI backbone that does not contain ABC (e.g. TDF/FTC). This regimen may be supplied regionally by GSK or reimbursement will be provided.

Switch of background NRTI therapy to an alternative approved NRTI therapy for toxicity or tolerability management is allowed once during the study. Switches of a background NRTI for any other reason are not permitted in the study. The date of the decision to switch background NRTI for toxicity or tolerability management must be documented in the eCRF.

If a subject needs to change background NRTI therapy for toxicity management, an alternative FDC (e.g. TDF/FTC) should be considered first. If this switch is not possible or appropriate, alternative approved dual NRTI therapy may be considered after consultation with the study medical monitor. This regimen may be supplied regionally by GSK or reimbursement will be provided.

Local prescribing information should be consulted for information regarding use of these medications.

NOTE: When applying the MSDF algorithm (also known as the Snapshot algorithm), subjects switching background NRTIs after Week 2 may be considered a non-responder, however, these subjects will be allowed to continue in the study.

5.6.1. Oral Bridging

In exceptional circumstances, the medical monitor may authorize the use of oral CAB 30 mg and/or RPV 25 mg as a short-term "bridging" strategy for subjects who have begun CAB LA + RPV LA. This strategy would only be employed to address any potential gap in CAB LA + RPV LA dosing as a result of unexpected scheduling conflicts which would prevent planned dosing. Should a subject need "oral bridging", sites must contact the medical monitor for authorization and guidance for treatment

strategies prior to a missed CAB LA + CAB LA dose. Should a subject not notify the site in advance, the medical monitor must be contacted for further treatment guidance.

5.7. Interruption of Study Treatment and Visit/Dosing Windows

IP or background NRTI may be interrupted at the discretion of the Investigator in the event of an AE, according to the severity of the AE.

If one or more antiretroviral medications is held due to toxicity or adverse events, all antiretroviral medications must be held to reduce the risk of development of resistance taking into account both the length of the planned interruption and the pharmacokinetic half-life of each antiretroviral of the regimen, in a way to minimize the risk of development of resistance.

It is important to note that keeping to the subject's visit schedule is a very important component to the study.

Note: **All decisions regarding dose interruption / resumption must be discussed with the medical monitor in advance.**

5.7.1. Oral Dosing Including Long Term Follow Up

Visits for subjects on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit.

Any interruption in therapy (scheduling conflicts, life circumstances, etc) during any oral dosing period that is greater than 7 consecutive days must be discussed with the medical monitor prior to resumption of therapy. The medical monitor must be contacted upon site staff becoming aware of resumption in therapy, if therapy was resumed without prior approval.

Visits for subjects in Long Term Follow Up are expected to occur as projected according to the last injection. There is a (+ or -) 3 day visit window, from the projected visit date.

5.7.2. IM Dosing

Subjects receiving CAB LA and/or RPV LA are anticipated to be at high risk for development of virologic resistance if ART is interrupted. The time period during which subjects are at risk for development of virologic resistance may be determined by the period between when drug levels fall below therapeutic values and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and is dependent upon effective concentration, inhibitory concentration and half-life. Plasma concentrations of both drugs may be measurable for approximately 52 weeks following IM injections.

IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred. At one-week post dose visits (Week 1, Week 25, and Week 41), there is no defined visit window, rather visits should occur approximately 1 week from the last injection.

- Dosing may occur without consultation from the medical monitor if performed within the (+ or -) 7 day window.
- Any request for the visit/dosing to occur outside of the allowed window must be discussed and agreed with the medical monitor *prior* to dosing. In the event of a late dose, a revised dosing schedule for subsequent dosing may be required and will be communicated to the site staff at the time of approval for continued dosing. Temporary switch to oral dosing of CAB 30 mg and/or RPV 25 mg may be an option based on individual subject circumstance as described in Section 5.6.1.
- See the SPM for scheduling guidance and further information and examples.

Note: **All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**

5.8. Discontinuation of Study Treatment

Subjects unable to manage drug toxicity or tolerate investigational product must have IP discontinued.

5.8.1. Discontinuation of ABC/3TC

In the event of a discontinuation of an ABC-containing product for any reason, re-initiation of this drug should be undertaken with caution. Health care providers should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product. If there are symptoms consistent with a hypersensitivity reaction, ABC must not be reinitiated. If there is no evidence of a prior reaction, the subject may restart treatment with the ABC-containing product. The subject and health care provider must be aware of the possibility of a rapid-onset hypersensitivity reaction upon reinitiation of ABC, which may be life-threatening or fatal, and the subject must be able to, if necessary, receive prompt medical evaluation (see also Section 6.10.6.14).

5.8.2. Discontinuation of CAB LA or RPV LA

Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the Long-Term Follow-Up Period for 52 weeks of follow up (see Section 5.8.2).

5.9. Concomitant Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must be advised to notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.

5.9.1. Permitted Medications and Non-Drug Therapies

Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of plasma HIV-1 RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment.

Other IM injectables (with exceptions below) are permitted but must be administered away from the site of IP administration.

Oral administration only: Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB and RPV, and H2-antagonists must be taken at least 12 hours before or at least 4 hours after taking CAB and RPV.

Concurrent administration of multivitamins is acceptable.

5.9.2. Prohibited Medications and Non-Drug Therapies

HIV immunotherapeutic vaccines are not permitted at any time during the study.

Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria #24, Section 4.3).

Systemically administered immunomodulators are prohibited.

Acetaminophen cannot be used in patients with acute viral hepatitis.

Chronic use of oral glucocortioids must be avoided; however, short treatment courses (e.g., 10 days or less) and topical, inhaled or intranasal use of glucocortioids will be allowed.

Hepatitis C infection therapy is allowed during the study, but interferon-based HCV therapy is prohibited throughout the entire study. Options for treatment of hepatitis C must be discussed with the Medical Monitor prior to initiation of therapy.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen (e.g. Epzicom / Kivexa), please consult the local prescribing information.

5.9.2.1. Concurrent with CAB and/or RPV

For subjects receiving **either formulation** of CAB and/or RPV, the following medications could significantly decrease the levels of CAB and/or RPV due to enzyme induction and therefore must not be administered concurrently:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin / Rifampin
- Rifapentine
- St. John's wort

5.9.2.2. Concurrent with RPV

In addition, subjects must discontinue the following (or change to an allowable alternative) while receiving treatment with oral RPV:

- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;
- systemic dexamethasone (more than a single dose).

If the subject cannot discontinue use or change to an allowable alternative while receiving treatment with RPV, the subject should not be randomized into the study.

5.9.2.3. Concurrent with either CAB LA or RPV LA

In addition, for subjects receiving CAB LA and RPV LA, use of anticoagulation agents greater than 14 days are prohibited and systemic anticoagulation on the day of an IM injection should be avoided where possible.

5.10. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

All subjects who successfully complete the Maintenance Period will be considered for inclusion in the Extension Period (see Section 3.2.5).

5.10.1. Long-Term Follow-Up Period

Any subject who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen will enter the Long-Term Follow-Up Period (see Section 3.2.6). Since these subjects are anticipated to be at high risk for the development of virologic resistance if ART is interrupted, they must switch to an Investigator selected HAART regimen and remain on study for at least 52 weeks following their last dose of CAB LA and / or RPV LA.

Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating. Subjects will continue to be dosed according to the agreed regimen selection for 52 weeks.

GSK may supply HAART regionally or reimbursement will be provided

5.11. Treatment of Study Treatment Overdose

For subjects receiving CAB, any tablet intake exceeding a total daily dose of 30 mg will be considered an overdose. For subjects receiving RPV, any dose exceeding a total daily dose of 25 mg will be considered an overdose. For subjects receiving Epzicom / Kivexa, any tablet intake exceeding the protocol defined daily number of tablets (one tablet daily) will be considered an overdose.

For CAB LA and RPV LA, any single dose in excess of the studied doses will be considered an overdose.

Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the subject stay onsite for up to 2 hours post dose for safety monitoring and notifying the medical monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV concentrations.

For the purposes of this study, an overdose is not an AE (refer to Section 6.10.4.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 6.10.4.2).

If an overdose occurs and is associated with an adverse event requiring action, all study medications must be temporarily discontinued until the adverse event resolves.

The Investigator should use clinical judgement in treating overdose, as GSK is unable to recommend specific treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Time and Events Table – Induction Period

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
Written Informed Consent	X							a. Complete all Screening assessments within 28 days. Subjects may begin the Induction Period as soon as all Screening assessments are complete. Subjects may be rescreened once and will be assigned a new subject number. b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and / or care. c. Height collected at Baseline only. d. Measure vital signs after about 5 minutes of rest in a semi-supine position. e. Perform ECG at Baseline in triplicate prior to dosing; preferably 2 – 4 hours post dosing for all other visits. f. Collect full routine medical history plus (report at Baseline visit): HIV risk factors (may be collected at a later study visit), cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders. g. Collect SAEs at Screen only if associated to study participation. h. Confirmation of eligibility to enter the Maintenance Period. See Section 3.2.3.
Demography	X							
Eligibility Verification	X	X				X [h]		
Physical Exam [b]	X							
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X	X smoking status also	
Weight and Height [c]		X					X	
Vital Signs (BP, HR) [d]	X	X				X	X	
12-Lead ECG [e]	X	X pre-dose x3				X	X	
Medical History [f]	X							
Medication History / Prior ART History	X							
CDC Classification	X	X						
HIV Associated Conditions			X	X	X	X	X	
AE and SAE Assessment, Con Meds	X [g]	X	X	X	X	X	X	

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
Columbia Suicide Severity Rating Scale (eC-SSRS) [i]	X	X	X	X	X	X	X	i. Preferably completed at the beginning of the visit. j. Collect for women of childbearing potential only. A negative urine pregnancy test is required prior to beginning the Induction Period. S=Serum/U=Urine k. Plasma for storage will be used: to determine genotypic eligibility at Screen, for possible future analyses, as back- up in case samples are lost or damaged in transit to the lab and for genotypic and phenotypic analyses in cases of virologic failure. l. Overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable. m. Collect pharmacogenetics (PGx) sample at Baseline. May be collected later during the study if necessary.
HIVTSQ(s) [i]			X			X	X	
HIVMQ						X		
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	
Pregnancy Testing [j]	S	U	S	S	S	S	S	
HIV-1 RNA and sample for storage [k]	X and genotype	X	X	X	X	X	X	
CD4+	X	X	X	X		X	X	
CD8+		X				X		
Urinalysis		X				X	X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [l]		X				X	X	
Hepatitis B (HBsAg) and Hepatitis C (anti-HCV Ab), HLA-B*5701	X							
PT/PTT/INR	X	X						
PGx [m]		X						

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
PK Sample (S)torage							S	n. Instruct subjects to continue to take the Induction regimen (including RPV) through Day 1 of the Maintenance Period. Subjects should be reminded to take the Day 1 dose in the clinic for PK sampling and return the PK diary. The PK diary will be completed by all subjects in case they are randomized to continue on the CAB 30 mg + ABC/3TC arm. o. Remind subjects of the potential change in study treatment and visit frequency beginning at Day 1.
Study Treatment Dispensation		X	X	X	X	X [n] Add RPV		
Study Treatment Accountability (pill counts)			X	X	X	X	X	
PK Diary Dispensation						X [n]		
Subject Visit Reminder Contact	X	X	X	X	X	X [o]	X	
Subject Contact Detail Confirmation	X	X	X	X	X	X		
Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.								

6.2. Time and Events Table – Maintenance Period for IM Regimen (CAB LA+RPV LA Q8W)

Procedures For Maintenance – **Q8W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Verify Eligibility	X																												
Randomization	X																												
Symptom Directed PE, ISR & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X	X				X			X					X		X		X		X		X		X		X	X
Weight and BMI	X										X					X												X	X
ECG [c]	X[pre]	X	X	X				X			X[c]					X[c]				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Diary (D)aily/(E)pisodic)[d]	D	E	E	E	E	E	E	D	E	E	E	E	D	E	E	E		E		E		E		E		E		E	E
Exercise Habit Assessment [e]		X							X					X															
eC-SSRS [f]	X		X	X	X	X	X	X		X	X		X			X		X		X		X		X		X		X	X
HIVTSQ(s) [g]	X[pre]			X							X					X												X	X
HIVTSQ(c) [g]											X																		X
HIVMQ [g]				X							X					X												X	X [g]

Procedures For Maintenance – **Q8W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
Pregnancy Test (U)rine/(S)erum [h]	U		U	U	U	U	U	U		U	U	U	U		U	U		U		U		U		U		U		U	S
HIV-1 RNA & sample for storage[i]	X		X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
CD4+	X		X	X				X			X					X		X				X		X				X	X
CD8+	X										X					X												X	
Urinalysis	X										X					X						X						X	X
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X		X								X					X						X						X	X
PT/PTT/INR	X										X					X												X	X
PK Sample (S)torage [k]	X [k]	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X	X[k]		S		S		S		S		S		S	X
Study Treatment Administration [m]	X [l]		X	X		X		X			X		X			X		X		X		X		X		X		X[n]	
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index
Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including injection site reactions.

a) Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject. See Section 6.10.1 for ISR assessment requirements.
b) Measure vital signs after about 5 minutes of rest in a semi-supine position.
c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit. At Week 32 and Week 48, a second ECG will be obtained approximately 2 hours after the last injection and just prior to the 2 hour post dose PK sampling.
d) Subjects will complete a (D)aily diary of injection site reactions from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. At all other visits subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.
e) Subject's exercise habits will be assessed daily from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. Assessments will include type and duration of cardiovascular exercise and duration of any strength or other strenuous exercises. This information will be collected via the daily ISR diary and entered into the eCRF.
f) Preferably completed at the beginning of the visit.
g) Conduct the HIVTSQ(s) at Day 1 pre-dosing; at all other visits conduct post-dosing. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ post injection.
h) Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
i) Plasma for storage samples collected for possible analyses, back-up in case samples are lost or damaged in transit to lab, for geno/pheno analyses and virologic failures.
j) Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k) Take PK samples pre-dose except Weeks 1, 12, 20, 25, 28, 36, 41 and 44 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of CAB 30 mg+ABC/3TC+RPV 25 mg. A second Day 1, Week 32 and Week 48 PK sample will be collected approximately 2 hours after the last injection.
l) Subjects should take CAB 30 mg+ABC/3TC+RPV 25 mg on Day 1 in the clinic after PK sampling and injections should be administered within 2 hours of this where possible.
m) Subjects will take final dose of Induction regimen in the clinic at Day 1 and begin injections. Day 1 injections are 2 x CAB LA 400 mg IM + 1 x RPV LA 900 mg IM. Week 4 injection is 1 x CAB LA 600 mg IM (no RPV LA). At Week 8 and Q8W, injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing expected to occur during week subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from date of projected visit, is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the Medical Monitor in advance.**
n) Subjects will continue to receive their Maintenance Period dosing regimen in the Extension period (Q8W) at this visit.
o) Subjects who WD must enter Long-Term Follow Up (see Section 3.2.6) instead of completing the WD visit. If they cannot enter Long-Term Follow-Up complete WD and Follow Up assessments.
p) Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required for subjects not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by phone.

6.3. Time and Events Table – Maintenance Period for IM Regimen (CAB LA+RPV LA Q4W)

Procedures For Maintenance – **Q4W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Verify Eligibility	X																												
Randomization	X																												
Symptom Directed PE, ISR & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X	X				X			X					X		X		X		X		X		X		X	X
Weight and BMI	X										X					X												X	X
ECG [c]	X[pre]	X	X	X				X			X[c]					X[c]				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Diary (D)aily/(E)pisodic[d]	D	E	E	E	E	E	E	D	E	E	E	E	D	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Exercise Habit Assessment [e]		X							X					X															
eC-SSRS [f]	X		X	X	X	X	X	X		X	X		X			X		X		X		X		X		X		X	X
HIVTSQ(s) [g]	X[pre]			X							X					X												X	X
HIVTSQ(c) [g]											X																		X
HIVMQ [g]				X							X					X												X	X [g]

Procedures For Maintenance – **Q4W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
Pregnancy Test (U)rine/(S)erum [h]	U		U	U	U	U	U	U		U	U	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	S
HIV-1 RNA & sample for storage[i]	X		X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
CD4+	X		X	X				X			X					X		X				X		X				X	X
CD8+	X										X					X												X	
Urinalysis	X										X					X						X						X	X
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X		X								X					X						X						X	X
PT/PTT/INR	X										X					X												X	X
PK Sample (S)torage [k]	X	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X	X[k]		S		S		S		S		S		S	X
Study Treatment Administration [m]	X [l]		X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index

a) Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject. See Section 6.10.1 for ISR assessment requirements.
b) Measure vital signs after about 5 minutes of rest in a semi-supine position.
c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit. At Week 32 and Week 48, a second ECG will be obtained approximately 2 hours after the last injection and just prior to the 2 hour post dose PK sampling.
d) Subjects will complete a (D)aily diary of injection site reactions from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. At all other visits subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.
e) Subject's exercise habits will be assessed daily from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. Assessments will include type and duration of cardiovascular exercise and duration of any strength or other strenuous exercises. This information will be collected via the daily ISR diary and entered into the eCRF.
f) Preferably completed at the beginning of the visit.
g) Conduct the HIVTSQ(s) at Day 1 pre-dosing; at all other visits conduct post-dosing. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ post injection.
h) Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
i) Plasma for storage samples collected for possible analyses, back-up in case samples are lost or damaged in transit to lab, for geno/pheno analyses and virologic failures.
j) Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k) Take PK samples pre-dose except Week 1, Week 25 and Week 41 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of CAB 30 mg+ABC/3TC+RPV 25 mg. A second Day 1, Week 32 and Week 48 PK sample will be collected approximately 2 hours after the last injection.
l) Subjects should take CAB 30 mg+ABC/3TC+RPV 25 mg on Day 1 in the clinic after PK sampling and injections should be administered within 2 hours of this where possible.
m) Subjects will take final dose of Induction regimen in the clinic at Day 1 and begin injections. Day 1 injections are 2 x CAB LA 400 mg IM + 1 x RPV LA 600 mg IM. At Week 4 and Q4W, injections are 1 x CAB LA 400 mg IM + 1 x RPV LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from date of projected visit, is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
n) Subjects will continue to receive their Maintenance Period dosing regimen in the Extension period (Q4W) at this visit.
o) Subjects who WD must enter Long-Term Follow Up (see Section 3.2.6) instead of completing the WD visit. If they cannot enter Long-Term Follow-Up complete WD and Follow Up assessments.
p) Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required for subjects not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by phone.

6.4. Time and Events Table – Maintenance Period for Oral Regimen (CAB 30 mg+ABC/3TC)

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Verify Eligibility	X																								X [k]	
Randomization	X																									
Symptom Directed PE & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X				X		X				X		X		X		X		X		X		X	X
Weight and BMI [c]	X								X				X												X	X
ECG [c]	X pre	X	X				X		X				X				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Diary (D)ispensation and (R)eview [d]	R							D	R			D	R												D	
eC-SSRS [e]	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X	X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
HIVTSQ(s) [f]	X pre		X						X				X												X	X
HIVTSQ(c) [f]									X																	X
HIVMQ [f]			X						X				X												X	X [f]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X
Pregnancy Test (S)erum/(U)rine [g]	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S		S		S		S		S	S
HIV-1 RNA & sample for storage [h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X [m]	X
CD4+	X	X	X				X		X				X		X				X		X				X	X
CD8+	X								X				X												X	
Urinalysis	X								X				X						X						X	X
Fasting: Glucose, Insulin, Cholesterol (Total, HDL and LDL) and Triglycerides [i]	X	X							X				X						X						X	X
PT/PTT/INR	X								X				X												X	X
PK Sample [j]	X								X				X												S	X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Study Treatment Dispensation and Accountability [n]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X [q]	
Study Treatment Administration																										
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X[l,o]	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index

Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including compliance.

a. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.

b. Measure vital signs after about 5 minutes of rest in a semi-supine position.

c. 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, it is preferable to conduct 2 – 4 hours after dosing.

d. Review PK diary at the beginning of the visit to verify time of last dose. PK samples must be collected within the window of 20-28 hours after the last dose taken. Contact the study team for guidance in cases when subject's last dose is not within window. Visit may need to be rescheduled.

h. Plasma for storage samples are collected for possible future analyses, as back- up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures

i. Fast overnight; however, a minimum of a 6 hour fast is acceptable.

j. All PK samples should be taken pre-dose within 20-28 hours after the last dose of IP taken. Subjects will take their dose of IP in the clinic at PK visits. S=Storage

k. Assess subject's willingness to continue on to the Extension Period. If not continuing into the Extension Period, this is the subject's last study visit.

l. For subjects continuing into the Extension Period only.

m. The Week 96 HIV-1 RNA result (or single re-test prior to Week 100) must be <50 c/mL to be eligible to continue into the Extension Period. See Section 3.2.5.2. Subjects ineligible for Extension will end their study participation at Week 96 (withdrawal visit needed).

e. Preferably completed at the beginning of the visit.

f. Conduct the HIVTSQ(s) at Day 1 prior to dosing and post dosing where possible at all other visits. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ preferably at the beginning of the visit, but may be completed at any time during the visit.

g. Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.

n. Subjects will discontinue RPV at Day 1 and begin taking 1 x CAB 30 mg + 1 x ABC/3TC tablet once daily. At Week 96, while awaiting eligibility for Extension, subjects will continue their CAB 30 mg+ABC/3TC regimen.

o. Remind subjects of the change in study and assessments for eligibility into Extension.

p. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.

q. Assess Treatment Accountability only

6.5. Time and Events Table – Extension Period for IM Regimen (CAB LA + RPV LA-Q8W)

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "a" for continuation of visit schedule after Week 200. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [c]	X		X	X			X		X		X		X		X		X	a. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 192, Week 216 will be conducted just like Week 200 and Week 224 will be conducted just like Week 192.
Weight & BMI	X		X	X			X		X		X		X		X		X	b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG [d]	X		X	X			X		X		X		X		X		X	c. Measure vital signs after about 5 minutes of rest in a semi-supine position.
Clinical Chemistry and Hematology	X	X	X	X	X [n]	X	X		X		X		X		X		X	d. Can be done at any time during the visit.
Pregnancy Testing (U)rine [e]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	e. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD.
																		f. Plasma for storage samples are collected

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
HIV-1 RNA and sample for storage [f]	X		X	X	X [n]		X		X		X		X		X		X	for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures. g. Fast overnight; however, a minimum of a 6 hour fast is acceptable. h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. A second Week 100 and 128 PK sample will be collected approximately 2 hours after the last injection. i. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. j. Q8W Injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption**
CD4+	X		X	X	X [n]		X		X		X		X		X		X	
Urinalysis	X		X	X	X [n]		X		X		X		X		X		X	
Fasting Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [g]	X		X	X	X [n]		X		X		X		X		X		X	
PT/PTT/INR																	X	
PK Diary (D)ispensation and (R)eview	R [n]																	
PK Sample (S)torage [h]	S	S	S	S	S [n]	S	S		S		S		S		S		X	
ISR Diary Dispensation [i]	E		E	E	E		E	E	E	E	E	E	E	E	E	E	E review	
Study Treatment Administration [j]	X [k]		X [k]	X	X		X	X	X	X	X	X	X	X	X	X		

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
																		must be discussed with the medical monitor in advance. k. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q8W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required. (W100=1st loading dose; W104=2nd loading dose) l. Or Long-Term Follow Up m. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone. n. Procedures and visits for subjects who switch from oral to the optimized Q8W IM dosing regimen. o. First Extension Period visit for subjects continuing Q8W dosing from the Maintenance Period.
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

6.6. Time and Events Table – Extension Period for IM Regimen (CAB LA + RPV LA - Q4W)

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "a" for continuation of visit schedule after Week 144. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [c]	X		X [m]	X [m]	X					X				X	X	
Weight & BMI	X		X		X					X				X	X	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG [d]	X		X [m]	X [m]	X					X				X	X	
Clinical Chemistry and Hematology	X	X	X	X	X	X [m]	X [m]	X	X [m]	X				X	X	
Pregnancy Testing (U)rine [e]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	
HIV-1 RNA and sample for storage [f]	X		X	X	X	X [m]	X [m]		X [m]	X				X	X	
CD4+	X		X	X	X	X [m]	X [m]		X [m]	X				X	X	

a. Continue this pattern for visits for the remainder of the study. For example, Week 148 will be conducted just like Week 132, Week 152 will be conducted just like Week 136, Week 156 will be conducted just like Week 140 and Week 160 will be conducted just like Week 144.
b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
c. Measure vital signs after about 5 minutes of rest in a semi-supine position.
d. Can be done at any time during the visit.
e. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD.
f. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
Urinalysis	X		X [m]	X [m]	X	X [m]	X [m]		X [m]	X				X	X	for virologic failures. g. Fast overnight; however, a minimum of a 6 hour fast is acceptable. h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. Week 100 PK sample should be taken after review of PK diary and pre-dose of CAB 30 mg+ABC/3TC. A second Week 100 and Week 128 PK sample will be collected approximately 2 hours after the last injection. i. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. j. Q4W Injections are 1 x CAB LA 400 mg IM + 1 x RPV LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.** k. Or Long-Term Follow Up l. Follow Up Visit - Conduct ~4 weeks after the last
Fasting Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [g]	X		X [m]	X [m]	X	X [m]	X [m]		X [m]	X				X	X	
PT/PTT/INR															X	
PK Diary (D)ispensation and (R)eview	R [m]															
PK Sample (S)torage [h]	S	S	S	S	S	S [m]	S [m]	S	S [m]	S				S	X	
ISR Diary Dispensation[i]	E		E	E	E	E	E		E	E	E	E	E	E	E review	
Study Treatment Administration [j]	X [n]		X	X	X	X	X		X	X	X	X	X	X		
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
																dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone. m. Procedures and visits for subjects who switch from oral to the optimized Q4W IM dosing regimen. n. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q4W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required.

6.7. Time and Events Table – Long-Term Follow Up Period

Procedures for Long-Term Follow Up	Month 1 [a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	Every effort should be made to enter subjects into the Long-Term Follow Up if they withdraw from or discontinue the study after receiving at least one dose of CAB LA and / or RPV LA. a) The start of the 52-week follow up period begins the day of the last CAB LA and/or RPV LA dose. b) Women of childbearing potential only. S = Serum c) Fast overnight; however, a minimum of a 6 hour fast is acceptable. d) Women of childbearing potential should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up Period. e) **Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating. This regimen may be supplied regionally by GSK or reimbursement will be provided.**
HIV-1 RNA	X	X	X	X	X	X	
CD4+	X	X	X	X	X	X	
Plasma for Storage	X	X	X	X	X	X	
PK Sample for Storage	S	S	S	S	S	S	
Clinical Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [b]	S	S	S	S	S	S	
Urinalysis	X				X	X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [c]					X	X	
PT/PTT/INR					X	X	
Contraception Counselling [d]	X	X	X	X	X	X	
HAART Dispensation [e]	X	X	X	X	X	X	

6.8. Critical Screening and Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject by study site personnel **prior** to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the Institutional Review Board/Institutional Ethics Committee (IRB/IEC). After signing an informed consent, subjects will complete Screening assessments to determine subject eligibility. Each subject being screened for study enrollment evaluation will be assigned a subject number. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by GSK.

Subjects must be counseled on the practice of safer sexual practices including the use of effective barrier methods (e.g. male condom/spermicide) and the length of time in which they are required for participation in this study as part of the eligibility process.

6.8.1. Screening

All clinical and laboratory assessments of eligibility must be performed and reviewed within 28 days of initiating the Screening process. All Screening results must be available prior to randomization.

Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the first Induction Period visit prior to enrollment.

Subjects may enroll and begin the Induction Period as soon as all Screening assessments are complete and the results are available and documented.

Each subject screened will be assigned a subject number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new subject number. Subjects who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

At Screening, samples for HIV-1 genotypic and phenotypic resistance testing and plasma HIV-1 RNA measurement will be obtained.

Subjects infected with HBV will not be enrolled in the study. Subjects with an anticipated need for HCV therapy during the study must not be enrolled into this study, as HCV therapy currently includes the prohibited medication interferon. The length of this study should be considered when assessing the potential need for therapy.

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF.

The electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) (see Section 6.10.10) assessed at the Screening visit will assess the subject's lifetime risk (any suicidal ideation, behavior, etc occurring over the subject's lifetime). A positive alert (indicating some risk) is not necessarily exclusionary, rather a means to assess overall risk.

6.8.2. Baseline

Subjects will have "Baseline" assessments completed at the beginning of the Induction Period.

Any changes to the eligibility parameters must be assessed and any results required must be available and reviewed prior to enrollment (e.g. urine pregnancy test for women of child bearing potential).

HIV-1 genotypic resistance testing and plasma HIV-1 RNA measurement results from Screening must be available prior to the Baseline visit.

In addition to a full routine medical history, more detailed information will be collected for some disease processes such as:

- cardiovascular risk factors (assessments will include smoking status and history; family history of cardiac events;
- history of illicit drug use [e.g. cocaine, heroin, and methamphetamine use]);
- intravenous drug use history;
- gastrointestinal disease (e.g. GI bleeding, PUD, etc);
- metabolic (e.g. Type I or II diabetes mellitus);
- psychiatric (e.g. depression);
- renal (e.g. nephrolithiasis, nephropathy, renal failure); and,
- neurologic disorders.

6.9. Efficacy

6.9.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 6). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases (e.g., where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods will be used to further characterize HIV-1 RNA levels.

6.9.2. Lymphocyte Subsets, CD4+ and CD8+

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to Time and Events schedule (Section 6) and Labroatory Assessments (Section 6.10.2).

6.9.3. HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events schedule (Section 6). HIV-associated conditions will be assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (see Section 11.1). Indicators of clinical disease progression are defined as:

CDC Category A at enrollment → Category B event;

CDC Category A at enrollment → Category C event;

CDC Category B at enrollment → Category C event;

CDC Category C at enrollment → New Category C Event;

CDC Category A, B or C at enrollment → Death.

6.10. Safety

6.10.1. Clinical evaluations

The following clinical evaluations will be performed according to the Time and Events schedule (see Section 6):

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 6.10.12.
- Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height and weight will be measured and recorded. Height collected on the first day of the Induction Period only.
- Vital Signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes.
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- Exercise habits will be assessed for subjects on the CAB LA+RPV LA regimen.
- HIV-associated conditions will be recorded.
- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position. At the first day of the Induction Period, ECGs should be performed in triplicate prior to first dose. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each subject. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations.

- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids (parameters to be tested listed below).
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the medical monitor following a treatment interruption(s).
- Evaluation and documentation of all concomitant medications and blood products.
- Injection Site Reactions (ISRs) will be assessed for the following clinically as well as patient-reported by utilizing a subject diary:
    - Daily from Day 1 – 7, from Week 24 – Week 25 and again daily from Week 40 to Week 41: Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).
    - Episodic (as reported by subject) for the Maintenance and Extension Period for the above parameters
    - The investigator should utilize subject diary reports to assist with a clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale). A clinical assessment should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, including those reported by the subject via diary, will be documented in the ISR AE eCRF. Daily diary data, or subject assessment, will be documented verbatim in the diary eCRF.
- Columbia Suicide Severity Rating Scale (eC-SSRS) will be assessed as per the Time and Events Schedule (see Section 6 and Section 6.10.10).

Any appropriately qualified site personnel (e.g., Investigator, sub-Investigator, or study coordinator/nurse) can perform assessments.

6.10.2. Laboratory Assessments

All protocol required laboratory assessments, as defined in the Time and Events Schedule (see Section 6), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

Refer to the lab manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Labs will be automatically graded by the central lab according to the DAIDS toxicity scales (See Section 11.2 “Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”).

For fasting laboratory assessments, an overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable.

Following are the lab parameters to be assessed as per the Time and Events Schedule (see Section 6):

Hematology		**Chemistry**		
Platelet Count	Automated WBC Differential:	BUN	Total CO_2	Total bilirubin[a]
RBC Count	Neutrophils	Creatinine[b]	Lipase	Albumin
WBC Count (absolute)	Lymphocytes	Glucose[d]	AST	Creatine phosphokinase
Hemoglobin	Monocytes	Sodium	ALT	Total Cholesterol[d]
Hematocrit	Eosinophils	Potassium	Alkaline phosphatase	HDL and LDL Cholesterol[d]
MCV	Basophils	Chloride		Triglycerides[d]
Other Laboratory Assessments				
Plasma HIV-1 RNA and sample for storage	Hepatitis B (HBsAg) and Hepatitis C (anti-HCV Ab)[e] **at Screening only**	Urine Pregnancy test for women of child bearing potential	Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)	
CD4+ and CD8+ cell counts [CD4/CD8 ratio][c]	HLA-B*5701 **at Screening only**	Urinalysis and urine microalbumin/creatinine ratio	Pharmacogentics Sample (PGx)	

a) Direct bilirubin will be reflexively performed for all total bilirubin values > 1.5X ULN.
b) Creatinine clearance will be estimated by the central laboratory and assessed at Screening, Baseline, Week (-12), Week (-4), Day 1 and Weeks 4, 16, 32, 48 and 96.
c) CD8+ cells will only be reported at Baseline, Week (-4), Day 1 and Weeks 32, 48 and 96.
d) Fasting overnight preferred; 6 hour fast is acceptable.
e) HCV RNA may be requested through the central lab within 2 weeks of a positive anti-HCV antibody test.

6.10.3. Liver Chemistry Stopping and Follow up Criteria

6.10.3.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the follow-up period. IP will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin, bilirubin fractionation required).

NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria.

- ALT ≥8xULN.
- ALT ≥3xULN (if Baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x Baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists ≥2 weeks (with bilirubin <2 ULN & no signs or symptoms of acute hepatitis or hypersensitivity).
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, sites should **evaluate the presence of detectable urinary bilirubin on dipstick**, which indicates direct bilirubin elevations and suggests liver injury.

6.10.3.2. Liver Chemistry Stopping Criteria, Subject Management

Subjects who develop ALT ≥5xULN must be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When any of the liver chemistry stopping critera is met, do the following:

- Immediately hold IP.
- Report the event to the medical monitor within 24 hours of learning its occurrence (Section 6.10.12, Section 6.10.14).
- Complete the liver event eCRF and SAE eCRF, where applicable, (see Section 6.10.12).
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (described below), and monitor the subject until liver chemistries resolve, stabilize, or return to Baseline values as described below.
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within Baseline values.

Make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - HBsAg and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test). The site must contact GSK when this test is required. Please refer to the central laboratory manual.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

6.10.3.3. Liver Chemistry Stopping Criteria - Rechallenge

Subjects who meet liver toxicity stopping criteria should not be retreated with investigational product unless an exemption has been approved by the ViiV Safety and Labeling Committee (VSLC). The guideline for Rechallenge/Restart approved by the

VSLC, which is maintained as a separate document (See Section 11.4, Appendix 4), must be followed.

Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug or continuation of LA dosing is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.

Subjects approved by the VSLC for restarting or re-dosing IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

See Section 11.4, Appendix 4 for further details.

6.10.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.10.4.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.
- All injection site reactions.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.10.4.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record the presence of detectable urinary bilirubin on dipstick which may indicate direct bilirubin elevations and may suggest liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.10.5. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.10.6. Specific Toxicities / Adverse Event Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (See Section 11.2 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events"). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 6.10.12, "Adverse Events".

6.10.6.1. Treatment Interruption Due to an Adverse Event

The AE profile for CAB in combination with ABC/3TC or in combination with RPV has not yet been fully defined. IP or background NRTI may be interrupted at the discretion of the Investigator and according to the severity of the AE. If one or more antiretroviral medications is held due to toxicity or adverse events, all antiretroviral medications must be held to reduce the risk of development of resistance taking into account both the length of the planned interruption and the pharmacokinetic half-life of each antiretroviral of the regimen, in a way to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. IP and background NRTIs should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of IP or temporary interruption of one or more but not all drugs within the ART regimen should be made with the

understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Any interruption in therapy during the Maintenance Period, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the medical monitor prior to resumption of therapy. The medical monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval (Section 5.7). **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred.** Any interruption outside of this guidance MUST be discussed with the medical monitor prior to reinitiating IM IP (see Section 5.7.2).

Guidance is provided below on general subject management and IP interruptions based on the severity of the AE. Information regarding permitted substitutions of background therapy is provided in Section 5.6. All changes in the IP or background NRTI regimen must be accurately recorded in the subject's eCRF.

In the event of a discontinuation of an ABC-containing product for any reason, re-initiation of this drug must be undertaken with caution. Health care providers should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product. If there are symptoms consistent with a hypersensitivity reaction, ABC should not be reinitiated. If there is no evidence of a prior reaction, the subject may restart treatment with the ABC-containing product. The subject and health care provider should be aware of the possibility of a rapid-onset hypersensitivity reaction upon reinitiation of ABC, which may be life-threatening, and the subject should be able to, if necessary, receive prompt medical evaluation (see also Section 6.10.6.14).

6.10.6.2. Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the Investigator. (NOTE: See Section 6.10.6 "Specific Toxicities/Adverse Event Management" for exceptions to this guideline). Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Subjects who develop a Grade 1 or 2 AE or toxicity, which the Investigator considers related or possibly related the background NRTI medications, may be addressed by substitution with another approved NRTI combination **one time** during the study, as described in Section 5.6 "Protocol-Permitted Substitutions".

6.10.6.3. Grade 3 Toxicity/Adverse Event

Subjects who develop a Grade 3 AE or toxicity should be managed as follows:

- If the Investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with GSK medical monitor.

- Subjects who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.
- Should the same Grade 3 AE recur within 28 days in the same subject, the IP should be permanently discontinued and the subject withdrawn from study.
- Subjects experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of IP. Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.
- Subjects who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to one of the background ART medications may be addressed by substitution of the medication for another approved compound in the same class (e.g., a switch of ABC/3TC FDC for TDF/FTC FDC) one time during the study, as indicated in Section 5.6 "Protocol-Permitted Substitutions." Subjects should be rechecked each week until the AE returns to Grade 2.
- Subjects with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with GSK medical monitor, may continue if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 6.10.3). Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

6.10.6.4. Grade 4 Toxicity/Adverse Event

- Subjects who develop a Grade 4 AE or toxicity must have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with and assent from GSK. Subjects should be rechecked each week until the AE returns to Grade 2.
- Grade 4 AEs that the Investigator considers related or possibly related to one of the background ART medications may be addressed by substitution of the medication for another approved compound in the same class (e.g., a switch of ABC/3TC FDC for TDF/FTC FDC) one time during the study, as indicated in Section 5.6 "Protocol-Permitted Substitutions". Subjects should be rechecked each week until the AE returns to Grade 2.
- Subjects experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above. Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue

IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.

- Subjects with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with GSK, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 6.10.3). A follow-up visit should be performed 4 weeks after the last dose of study medication if AEs or laboratory abnormalities are ongoing.

6.10.6.5. Diarrhea

Subjects with Grade 1 or 2 diarrhea may continue study treatment without interruption. Subjects with diarrhea of any toxicity grade may be treated symptomatically with anti-motility agents; however, the recommended daily dose of the chosen anti-motility agent must not be exceeded. If symptoms persist or get worse on the recommended daily dose of the chosen anti-motility agent, then the anti-motility agent must be discontinued and consultation made with GSK.

For subjects with Grade ≥3 diarrhea that is unresponsive to the recommended dose of the anti-motility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, the treatment with the anti-motility agent and IP must be interrupted until resolution of diarrhea to Grade ≤2 or Baseline, after which IP and background ART may be resumed after discussion and agreement with GSK. If Grade ≥3 diarrhea recurs within 28 days upon the resumption of IP, the IP should be permanently discontinued and the subject withdrawn from the study. Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.

If loperamide is used for treatment of diarrhea, local prescribing information should be followed with respect to dose and frequency of administration. Loperamide dosing should not exceed local prescribing information.

6.10.6.6. Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements **must** be obtained in a fasted state according to the Time and Events table (Section 6). Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP. Clinical management of subjects with hypertriglyceridemia/hypercholesterolemia should **not** be based upon non-fasting samples (obtained in the fed state). A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia. Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

Please see the Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group [Dube, 2003] for full discussion of management of hyperlipidemia in the context of HIV therapy.

6.10.6.7. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.

Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued and the subject withdrawn from the study. Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the Long-Term Follow-Up Period for 52 weeks of follow up.

6.10.6.8. Lipase Elevations and Pancreatitis

Subjects with asymptomatic Grade 1 or 2 elevations in lipase may be followed closely for the development of symptoms.

Subjects with asymptomatic Grade ≥3 elevations in lipase that are considered possibly or probably related to IP should have IP interrupted until serum lipase returns to Grade ≤2. The lipase assay should be repeated within 2 weeks of any Grade ≥3 result. Subjects with persistence of Grade ≥3 lipase in the absence of other diagnoses or reoccurrence of lipase elevation (at Grade ≥2) following reintroduction of IP should permanently discontinue IP.

Subjects with a confirmed diagnosis of clinical pancreatitis that is considered possibly or probably related to IP should have IP held. After complete resolution of the episode, subjects may be re-challenged with IP after discussion with the medical monitor, only if the Investigator has compelling evidence that the event was not caused by IP. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the subject should discontinue IP and be withdrawn from study.

Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.

6.10.6.9. Decline in Renal Function

The following criteria are defined based on Cockcroft-Gault estimates of GFR. The Cockcroft-Gault criteria are based on recommendations for changes in dosing administration for both ABC/3TC FDC and TDF/FTC FDC. Current local prescribing information should be consulted for additional details on dosing in renally impaired subjects.

Subjects who experience progression to an estimated GFR (calculated by Cockcroft-Gault equation) of <50 mL/min must return for a confirmatory assessment within 4 weeks. A urinalysis should also be done at this confirmatory visit. If an estimated GFR of <50 mL/min is confirmed, any subjects receiving TDF/FTC FDC must be switched to an alternative nucleoside combination at the discretion of the Investigator and medical monitor. Subjects on ABC/3TC FDC may switch to the individual components dose adjusted for renal dysfunction according to approved prescribing information, or switch to alternative nucleosides at the discretion of the Investigator and GSK Medical Monitor.

Proximal Renal Tubule Dysfunction (PRTD) is defined as:

- Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL
- Either of the above accompanied by any two of the following:
- Glycosuria (≥250 mg/dL) in a non-diabetic
- Low serum potassium (<3 mEq/L)
- Low serum bicarbonate (<19 mEq/L)

Subjects meeting criteria for PRTD must return for a confirmatory assessment within 4 weeks. A urinalysis should be done at the time of the confirmatory assessment. If PRTD is confirmed subjects receiving TDF/FTC FDC must be switched to an alternative nucleoside combination. Subjects on ABC/3TC FDC may switch to the individual components dose adjusted for renal dysfunction according to approved prescribing information, or switch to alternative nucleosides at the discretion of the Investigator and GSK Medical Monitor.

6.10.6.10. Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (>0.3 mg/mg, >300 mg/g or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio performed within 2 to 4 weeks. If confirmed, then consideration should be made for additional evaluation after consultation with the Study medical monitor. Additional evaluation may include a 24 hr urine protein and creatinine measurement and nephrology referral.

Subjects with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g or>34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 μMol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study Medical Monitor should be immediately contacted. Further management should be agreed between the investigator and medical monitor.

6.10.6.11. QTc Prolongation

Subjects with an average QTc interval > 500 msec or a >60 msec increase from baseline, from three or more tracings separated by at least 5 minutes should have IP discontinued. These criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (~5-10 minutes) and use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study. If an alternative cause of the QT prolongation is determined (e.g., subject receiving drug known to cause prolonged QT or TdP), then IP may be restarted after consultation with and agreement by the Study medical monitor.

6.10.6.12. Injection Site Reactions (ISRs)

Injection site reactions will be managed through investigator assessment and subject diary collection throughout the study. All Grade 3 or 4 ISRs must be discussed with the medical monitor to determine etiology and assess appropriate continued study participation.

Digital photographs will be documented where possible on all subjects who have an injection site reaction that is either serious or Grade 2 or above that persist beyond 2 weeks. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.

ISR discomfort can be managed symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the subject's ability to perform activities of daily living. The required intervention should be documented on the appropriate eCRF page.

6.10.6.13. Allergic Reaction

Subjects may continue IP for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the IP should permanently discontinue the IP regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.

As EPZICOM is being used as background therapy, subjects should also be assessed for clinically suspected ABC hypersensitivity, as described below.

6.10.6.14. Abacavir Hypersensitivity Reaction (ABC HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the Local Country Prescribing Information for EPZICOM. Investigators must familiarize themselves with this information on ABC HSR in the Local Country Prescribing Information for each of these products prior to initiating subjects on ABC therapy.

Studies have shown that carriage of the *HLA-B*5701* allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

In any subject treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of *HLA-B*5701* status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ZIAGEN, EPZICOM/KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

6.10.6.14.1. Essential Patient Information

With reference to Local Country Prescribing Information and the 'Subject Information and Consent Form', Investigators must ensure that subjects are fully informed regarding the following information on the hypersensitivity reaction prior to commencing ABC therapy:

- Subjects must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased in individuals who are *HLA-B*5701* positive.
- Subjects must also be informed that *HLA-B*5701* negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY subject who develops

signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

- Subjects who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g. ZIAGEN, EPZICOM, KIVEXA or TRIZIVIR) again, regardless of their *HLA-B*5701* status.
- In order to avoid restarting abacavir, subjects who have experienced a hypersensitivity reaction should be asked to return any remaining EPZICOM / KIVEXA tablets to the Investigator or site staff.
- Subjects, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting EPZICOM / KIVEXA as more severe symptoms may recur within hours and may include life-threatening hypotension and death.
- Each subject should be reminded to read the Package Leaflet included in the EPZICOM / KIVEXA pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

6.10.6.14.2. Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH)-E2A, 1994 definitions of seriousness listed in Section 6.10.4.2 then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within one week of the onset of the hypersensitivity reaction. Clinically suspected cases of HSR to ABC that do not meet criteria as an SAE can be recorded as an AE.

6.10.6.15. Rash Without ABC HSR Symptoms

Including serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or rash with significant liver dysfunction

Subjects should be instructed to contact the Investigator as soon as possible if they develop a rash on study.

Subjects who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the

subject should not be re-challenged with any ABC-containing medicinal product (i.e., ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the subject is receiving should also be reviewed and discontinued as appropriate.

The following guidance is provided for clinical management of subjects who experience rash alone in the absence of accompanying diagnosis of ABC HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

Subjects with an isolated Grade 1 rash may continue IP and background ART at the Investigator's discretion. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Subjects may continue IP and background ART for an isolated Grade 2 rash. However, IP and background ART (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Subjects should permanently discontinue IP and background ART (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE. Any subject receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Period for 52 weeks of follow up.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (see Section 11.2).

If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

Any rash that is possibly related to study drug, and is present between Week (-4) and Day 1, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA.

6.10.6.16. Seizures

Seizures that occur on study should be managed according to the local guidelines on emergency seizure management which may include treatment with benzodiazepines, general supportive treatment, exclusion of metabolic and toxicological abnormalities using laboratory tests, and septic workup and excluding underlying structural abnormalities with neuroimaging.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses.

Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate eCRF page.

6.10.7. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

6.10.8. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

6.10.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with HIV-1 infection and can be serious/life threatening:

- events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Section 11.1)

- sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event). These events will be recorded on the DRE page in the subject's eCRF using the HIV Associated Conditions eCRF. These DREs will be monitored by the medical monitor, IDMC, and study team on routine basis.

However, if any of the following conditions apply, then the event should be reported as an SAE using the standard process:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product. or
- Death occurring for any reason during a study, including death due to a disease related event, will always be reported promptly. or
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV related

If either of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly (i.e., expedited reporting, see Section 6.10.12) to GSK.

6.10.10. Monitoring Suicidal Ideation and Behavior

Patients with HIV infection may occasionally present with symptoms of depression and/or suicidal ideation or behavior. Therefore, it is appropriate to monitor subjects prospectively for suicidal ideation and / or behavior before and during treatment. It is recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior.

Suicidal ideation or behavior will be monitored during this study using the electronic version of the Columbia Suicide-Severity Rating Scale (eC-SSRS). The behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Oquendo, 2003]. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The eC-SSRS is to be administered at the time-points specified in the Time and Events Table (see Section 6).

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the Adverse Event (Non-serious or Serious Adverse Events) eCRF form on any subject that experiences a possible

suicidality-related adverse event while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to GSK within one week of the investigator diagnosing a possible suicidality-related adverse event.

6.10.11. Pregnancy

6.10.11.1. Pregnancy Testing

Women of childbearing potential must have a negative pregnancy test at Screening, the first Induction Period visit and prior to administration of each CAB LA and / or RPV LA injection. Pregnancy testing will also be conducted as per the Time and Events Table (see Section 6) and at anytime during the trial when pregnancy is suspected.

Additionally, the medical monitor may request that a pregnancy test be performed in the event of a treatment interruption greater than 7 days.

6.10.11.2. Time Period for Collecting Pregnancy Information

Pregnancy information will be collected after the start of Induction until the last follow-up assessment. This includes the entirety of the Long-Term Follow-Up Period.

Female subjects that have received at least one dose of CAB LA or RPV LA and do not enter the Long-Term Follow-Up Period should use an acceptable method of contraception (see the SPM for a listing of examples of acceptable hormonal contraception) until at least 52 weeks after the last dose of study drug. If a subject becomes pregnant within 52 weeks of the last dose of study drug the subject should notify the study site.

6.10.11.3. Action to be Taken if Pregnancy Occurs

Any female who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue IP. Subjects who have received at least one dose of CAB LA and/or RPV LA should discontinue further dosing and continue oral HAART in the Long-Term Follow-Up Period (see Section 3.2.6), after discussion with the medical monitor.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

GSK's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

6.10.12. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.10.13.

6.10.13. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

6.10.14. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular (CV) or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
PRSAE	1 week	PRSAE data collection tool	1 weeks	Updated PRSAE data collection tool
Suspected ABC HSR[3]	24 hours	ABC HSR eCRF	1 Week	Updated ABC HSR eCRF
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities see Section 6.10.3[1,2]:				
ALT≥3xULN plus Bilirubin≥2xULN (35% direct)	24 hours	SAE data collection tool Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable	24 hours	Updated SAE data collection tool Updated Liver Event eCRF
ALT≥5xULN that persists ≥2 weeks	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF
ALT ≥8xULN	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT ≥3xULN or ALT ≥3 fold increase from Baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF

1. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety.
2. Liver Event Documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.
3. ABC HSR eCRF required only if event meets one of the ICH-E2A, 1994 definitions of seriousness (see Section 6.10.6.14.2).

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.10.14.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.11. Pharmacokinetics

Plasma samples for determination of CAB and RPV concentration will be collected throughout the Maintenance Period and from Week 100 – Week 128 in the Extension Period of the study for subjects switching from oral Maintenance period regimen to the optimized IM dosing regimen of their choice. Additional samples will be collected for storage during the Extension and Long-Term Follow Up Period. Samples for determination of RPV will be protected from light until analyzed.

6.11.1. PK Sample Collection

Blood samples for evaluation of CAB (2 mL each) and RPV (2 mL each) plasma PK will be collected from all subjects randomized to receive CAB LA + RPV LA for determination of CAB and RPV concentrations as described in Table 4. All PK samples will be collected prior to IM dosing and may be collected at anytime during visits that study treatment is not administered. The exact date and time of the PK sample should be recorded in eCRF.

For subjects randomized to CAB 30 mg, pre-dose blood samples for evaluation of CAB (2 mL each) and RPV (2 mL, Day 1 pre-dose only) will be collected as described in Table 4. These samples must be collected within the window of 20-28 hours after the last dose taken. Subjects will be expected to complete a PK dosing diary card noting the date and time of the last three doses of IP prior to the scheduled clinic visits on Day 1, Weeks 32, 48 and 100. The information from the diary card will be recorded in the eCRF. Additionally, dosing information on the clinic day, including whether or not the dose was administered with food, if the subject vomited within 4 hours of dosing and the actual date and time of the PK samples, must be recorded on the eCRF. Subjects will take their dose of oral IP in the clinic at PK visits.

Table 4 CAB and RPV Plasma Pharmacokinetic Sample Schedule

Group	Analyte	Week	Sample Times Relative to Dose
IM	CAB	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48 100* (prior to LA and last oral Maintenance dose), 104*, 108*, 112*, 116*, 120*, 124* and 128*	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40, 48, 100*, 104*, 112*, 120* and 128* Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 100*, 104*, 108*, 112*, 116*, 120*, 124* and 128* 2 Hours Post Dose: Day 1, Weeks 32, 48, 100*[a] and 128*[a] 1 Week Post Dose: Week 1, Weeks 25, 41, 101*[a] and Week 121*[a] 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
	RPV	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48 100* (prior to LA and last oral Maintenance dose), 104*, 108*, 112*, 116*, 120*, 124* and 128*	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40, 48, 100*, 104*, 112*, 120* and 128* Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 100*, 104*, 108*, 112*, 116*, 120*, 124* and 128* 2 Hours Post Dose: Day 1, Weeks 32, 48, 100*[a] and 128*[a] 1 Week Post Dose: Week 1, Weeks 25, 41, 101*[a] and Week 121*[a] 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
Oral	CAB	Day 1, Weeks: 32 and 48	Pre-Dose: Day 1, Weeks 32 and 48
	RPV	Day 1	Pre-Dose: Day 1

* Denotes PK sample times for subjects in the Extension Period. Samples will be placed in storage.
a. PK sample time for subjects switching from oral to an optimized IM dosing regimen only.

Additional CAB and RPV PK samples for storage will be collected pre-dose at Weeks 56, 64, 72, 80, 88 and 96 for subjects on CAB LA+RPV LA as per the Time and Events Table (see Section 6.2 and Section 6.3) and in the Extension Period (see Section 6.5 and Section 6.6). Samples for storage will also be collected at Week 96 subjects on CAB 30 mg+ABC/3TC, Weeks 100, 101, 104, 108, 112, 116, 120, 124 and 128 for subjects in the Extension Period, and at Months 1, 3, 6, 9 and 12 for subjects in the Long-Term Follow Up Period. These samples may be analyzed in case of protocol-defined virologic failure or to investigate any PK related issues (such as missing dose, missing sample, suspected non-adherence etc.).

In addition, if a subject withdraws from the study a PK sample should be collected as early as practically possible (i.e. at withdrawal visit or on the day the withdrawal decision was made).

Additional details concerning handling of PK samples, labeling and shipping directions will be supplied in the central laboratory manual.

6.11.2. Rationale of PK Sampling Strategy

Given that PK data has been collected following oral administration of CAB and RPV (LAI116482), there will be no sampling during the Induction Period of the study. Blood sampling for CAB and RPV concentrations will be performed during the Maintenance and Extension Periods of the study to evaluate PK in HIV infected subjects. The proposed PK visits and sampling scheme at each visit presented in Table 4 is based on consideration of available PK data to support interim and final PK and PK/Pharmacodynamic (PD) analysis planned in this study.

6.11.3. Bioanalysis of CAB and RPV

Plasma CAB analysis will be performed under the control of GSK PTSDMPK/ Scinovo. Concentrations of CAB will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for CAB any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK protocol.

Once the plasma has been analysed for RPV any remaining plasma may be used by the sponsor for further exploratory work on pharmacokinetics, metabolites, plasma protein binding, protein analysis, and biochemistry. No human DNA analysis will be performed.

Plasma CAB analysis will be performed under the control of Janssen R&D. Concentrations of CAB will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

6.12. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide "plasma for storage samples" according to the Time and Events Schedule in Section 6 (for potential viral genotypic and phenotypic analyses).

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for protease (PRO) and reverse transcriptase (RT), or with their GeneSeq Integrase and PhenoSense Integrase assays.

For Screening virologic evaluations, only viral genotype will be analyzed and this will be performed through the central laboratory.

6.12.1. HIV-1 pol Viral Genotyping and Phenotyping

At screening, samples will be collected for HIV-1 RT and PRO genotype using a Quest Diagnostics genotype assay and results will be provided to the Investigator to assist in the determination of subject eligibility.

Subjects experiencing confirmed virologic failure will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from both Baseline samples and from samples collected at the time of suspected virologic failure; these results will be reported to the Investigator as soon as available to provide guidance for election of a switch regimen.

6.12.2. HIV-1 Exploratory Analysis

Additional exploratory analyses for HIV-1 pol resistance may include viral genotyping and/or phenotyping on a representative subset of Baseline samples or virologic analysis on stored plasma samples from other time points. These analyses may also include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, super low HIV-1 RNA quantitation and measurement of viral replicative capacity. HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from all subjects who have HIV-1 RNA >200 c/mL regardless of confirmatory HIV-1 RNA.

6.13. Pharmacogenetic Research

Information regarding pharmacogenetic (PGx) research is included in Section 11.3.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Section 11.3). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx

assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

6.14. Health Outcomes

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) [Woodcock, 2001 and Woodcock, 2006] was developed to evaluate treatments for HIV and patient satisfaction. The higher the score, the greater the improvement in treatment satisfaction as compared to the past few weeks. A smaller score represents a decline in treatment satisfaction compared to the past few weeks. The HIVTSQ items are summed up to produce a treatment satisfaction score (0 to 60) and an individual satisfaction rating for each item (0 to 6) and two subscales: general satisfaction/clinical and lifestyle/ease subscales.

This study will be using the HIVTSQ(s) (status version) and the revised HIVTSQ(c) (change version). These measures will assess change in treatment satisfaction over time (in the same subjects) and compare current satisfaction with previous treatment satisfaction, from an earlier time point.

The HIV Medication Questionnaire (HIVMQ) was developed to assess subject reported medication adherence.

The HIVTSQ(s) will be administered at the following time points:

- Induction: Week -(-16) and Week (-4) (pre-dose if possible)
- Maintenance: pre-dose at Day 1, and post-dose (where possible in oral dosing arm) Week 8, Week 32, Week 48 and Week 96
- Withdrawal

The HIVTSQ(c) will be administered at the following time points:

- Maintenance: Week 32

The HIVTSQ(c, WD) will be administered at the following time points:

- Withdrawal for subjects withdrawn between Week 8 and Week 32

HIVMQ will be administered at the following time points:

- Induction: Week (-4)
- Maintenance: Week 8, Week 32, Week 48, Week 96 & Withdrawal
    - IM Regimen: Complete post-injection
    - Oral Regimen: Preferably completed at the beginning of the visit, but may be completed at any time during the visit.

Qualitative interviews with 20-30 subjects may be conducted regarding the subject's experience on the injection regimen. This would be conducted under a separate IRB/IEC approved consent. Participation in the interviews would be voluntary.

7. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The study is designed to evaluate the efficacy and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg IM every 8 weeks, relative to CAB 30 mg once daily plus ABC/3TC once daily, through Week 32 of the Maintenance Period.

To claim positive outcome, the following hypotheses will be tested:

H_0: Response rate for CAB LA plus RPV LA two-drug regimen ≤ CAB plus ABC/3TC -10%

H_1: Response rate for CAB LA plus RPV LA two-drug regimen > CAB plus ABC/3TC -10%

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

IM treatment relative to Oral treatment

The sample size of 45 subjects in the oral treatment arm and 90 subjects each in the IM treatment arms were chosen to ensure a high probability that a long-acting two drug treatment with truly poor response relative to CAB 30 mg once daily plus ABC/3TC once daily will not be studied further, while allowing for formal considerations of other factors should efficacy be similar between the treatment arms. It is assumed that 85% subjects enrolled will be suppressed at Week (-16), approximately 265 subjects will be enrolled in order to have 225 subjects randomized at Day 1.

The study is designed to test the comparability of CAB LA plus RPV LA two-drug regimen to CAB 30 mg once daily plus ABC/3TC. The primary comparison of interest will be performed using a Bayesian probability model. If the posterior probability that the difference is greater than -10% is large (i.e., ≥90%), then sufficient statistical evidence has been provided for the positive outcome. A response rate of 82% in the CAB LA plus RPV LA two-drug regimen (compared with an CAB 30 mg plus ABC/3TC response rate of 92%) would result in a rejection of the null hypothesis with a probability of approximately 0.064 (type I error). The given sample size is unlikely to select a random sample that would falsely conclude that CAB LA plus RPV LA two-drug regimen is comparable with CAB 30 mg plus ABC/3TC if the response rates are truly 82% versus 92%, respectively. If the CAB LA plus RPV LA two-drug regimen yields a response rate of greater than 92%, then there is a high probability of rejecting the null hypothesis and correctly concluding that CAB LA plus RPV LA two-drug regimen is at least as good as CAB 30 mg plus ABC/3TC.

Historical response rates of dolutegravir, an integrase compound similar to CAB, were used as reference for the oral control arm. Response rates for dolutegravir plus ABC/3TC ranged from 92% to 94% at Week 60 in studies SPRING-1, SPRING-2 and SINGLE among subjects who were suppressed (HIV-1 viral load <50 c/mL) at Week 24.

The probability of a positive outcome assuming the true response rate for CAB LA plus RPV LA two-drug regimen is presented in Table 5.

Table 5 Probability of Positive Outcome Assuming True Response Rates of CAB LA plus RPV LA

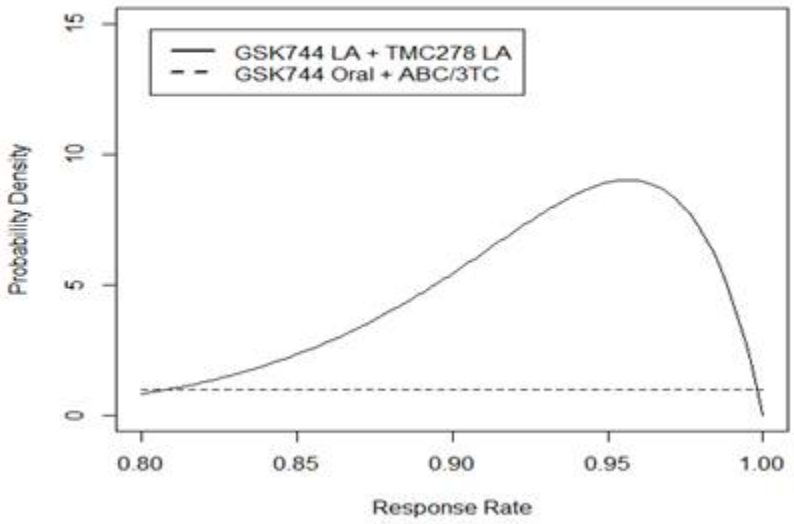
True Response Rate for CAB LA plus RPV LA two-drug regimen (Q4W or Q8W)	80%	82%[a]	86%	90%	92%	94%	96%
Probability of Positive Outcome[b]	2.8%	6.4%	26%	63%	82%	95%	99%

a. Type I error is <10%.
b. It is assumed that the response rate for CAB 30 mg plus ABC/3TC is 92%.

Incorporation of prior beliefs and information about population parameters is a required part of any Bayesian probability model. The assumptions made will help provide a more reliable estimate when the prior beliefs are combined with the observed data than the data alone as long as the beliefs are reasonable. Therefore, the trial will utilize a Beta (23, 2) distribution with the mean response rate being 92%, with 97.5th percentile of 99% and 2.5th percentile of 78%.

Furthermore, a non- informative prior belief is assumed for the response rate for CAB LA plus RPV LA two-drug regimen. Therefore, the trial will conservatively utilize a Beta (1, 1) distribution. These priors are displayed in Figure 15.

Figure 15 Plot of Prior Distribution for Response Rate for CAB LA plus RPV LA two-drug regimen and CAB 30 mg plus ABC/3TC



The posterior probability limit is used as a measure of evidence in support of a hypothesis. Selection of the critical value to base a decision of comparability can be made so that the type I error rate is controlled and the desired power profile is attained.

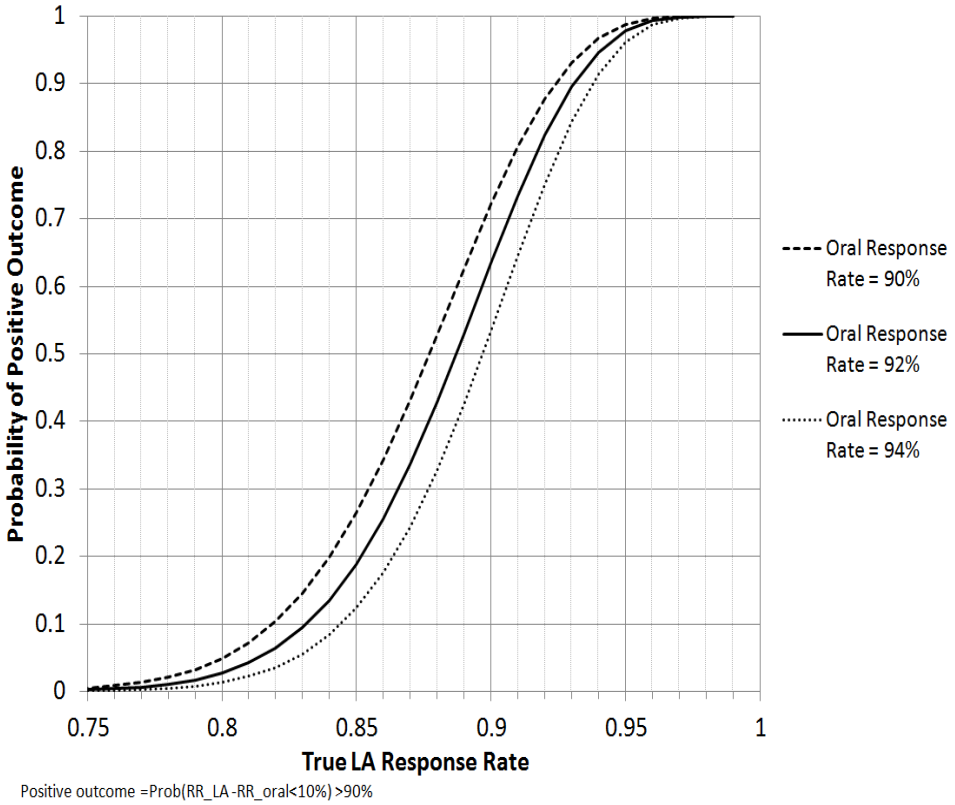
The total number of responders in each treatment arm (experimental and active control) is modelled as independent binomially distributed random variables. Conjugate beta priors are selected to reflect the beliefs about the response rates previously described.

8.2.2. Sample Size Sensitivity

Long Acting IM treatment relative to Oral treatment

The operating characteristic (power) curve is used to evaluate any decision criteria (Bayesian and non-Bayesian alike). The operating characteristic curve for the proposed sample sizes for each treatment arm and prior information is shown in Figure 16.

Figure 16 Operating Characteristic Curve of Probability of Positive Outcome of CAB LA plus RPV LA two-drug regimen and CAB 30 mg plus ABC/3TC



8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The following populations will be assessed:

8.3.1.1. Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all enrolled subjects who receive at least one dose of IP. Subjects will be analyzed according to their randomized treatment regardless of what treatment was actually received. Those that are not randomized will be summarized together under a 'Not Randomized' category. The ITT-E population will be the secondary population for some efficacy analyses.

8.3.1.2. Intent-to-Treat Maintenance Exposed Population (ITT-ME)

The ITT-ME population consists of all randomized subjects who receive at least one dose of IP during the Maintenance Period of the study. Subjects will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the ITT-ME population will be the primary population for efficacy analyses.

8.3.1.3. Per Protocol Maintenance Exposed Population (PP-ME)

This population will consist of subjects in the ITT-ME population with the exception of major protocol violators (these will be defined in the RAP of this study). The PP-ME population will be a secondary population for efficacy purposes.

8.3.1.4. PK Population

The PK Population will include all subjects who receive CAB and /or RPV and undergo PK sampling during the study, and provide evaluable CAB and /or RPV plasma concentration data. Subjects in this population will be included in the PK analysis.

8.3.1.5. Safety Population

The Safety Population consists of all enrolled subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not having consumed any amount of investigational product. Subjects will be analyzed according to the actual treatments received. Subjects will not be excluded from this population as a result of changes to the background regimen. The safety population will be the primary population for safety analyses. All safety analyses will be produced using the safety population.

Analysis populations for genotypic and phenotypic analyses will be described in the RAP.

8.3.1.6. Extension Switch Population

The Extension Switch population will include all subjects randomized to the oral 30 mg + ABC/3TC arm who switch to and receive at least one dose of the optimized IM dosing regimen of their choice (either Q8W or Q4W) in the Extension Period.

The Extension Switch population will be used to evaluate safety and efficacy of the optimized IM dosing regimens during the Extension Period.

8.3.2. Analysis Data Sets

The primary efficacy analysis data set will be based on the ITT-ME population described in Section 8.3.1.1. The efficacy dataset will include missing, switch, or discontinuation equals failure (MSDF) (also referred to as Snapshot), and the observed case (OC) endpoints for the proportion of subjects with plasma HIV-1 RNA less than the pre-

defined threshold (e.g., <200 c/mL and <50 c/mL). The MSDF endpoint will be considered the primary analysis approach and will be determined based on the current Food and Drug Administration (FDA) definition of the Snapshot algorithm. Full details on this algorithm will be contained in the RAP. The OC endpoint will not impute for any missing assessments. Details of the endpoint derivations will be described in the RAP for this study.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary efficacy analysis will be performed at Week 32 based on the proportion of subjects in the ITT-ME population with plasma HIV-1 RNA <50 c/mL using MSDF algorithm. The primary comparison of interest will be the response rate of each IM dosing arm to the oral control arm performed using a Bayesian probability model. The probability of (Response rate for IM arm > Response rate for Oral arm -10%) will be calculated.

8.3.3.2. Other Comparisons of Interest

The probability of Q8W comparable to Q4W will be provided using the Bayesian probability model.

Measures of safety and tolerability will be assessed as detailed in the RAP.

8.3.4. Planned Analysis

The ITT-ME population will be primary efficacy population and the safety population will be the primary safety population for all analyses. All available data will be included in all interim analyses, including data beyond the designated time point except for the Day 1 analysis, if preformed, will only include data from the Induction Period.

At the first interim analysis the IDMC will evaluate the efficacy, safety and tolerability of CAB to determine if the CAB regimen is suboptimal such that it should be discontinued before all subjects transition into the Maintenance Period of the study. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

This interim analysis schedule does not require an adjustment for multiplicity since there is no possibility of a false positive finding at any of the interim analyses conducted before Week 32, and since the Week 48 and 96 analyses will be used to further characterise the long-term safety and efficacy profile of CAB. As no hypothesis is being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity will be performed.

8.3.4.1. IDMC Interim Analyses

The purpose of these analyses is for the IDMC to evaluate the efficacy, safety and tolerability of CAB at early time points in the study and to monitor the occurrence of protocol defined virologic failure in subjects switching from oral CAB 30 mg +ABC/3TC to an optimized IM dosing regimens during the Extension Period.

The IDMC intends to review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period, or as soon as reasonably possible after subjects begin to enter the Maintenance Period. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter, with IDMC agreement.

All of the IDMC reviews will be produced by a Statistics and Data Analysis Centre (SDAC).

8.3.4.2. Futility Interim Monitoring

Continuous monitoring of the number of protocol defined virologic failures during the Maintenance Period and a futility interim analysis when 50% subjects have completed Week 24 is planned.

Continuous monitoring of the number of protocol defined virologic failures for subjects switching from oral CAB 30 mg + ABC/3TC to the optimized IM dosing regimen of their choice (Q8W or Q4W) will also be monitored during the Extension Period.

Continuous Monitoring

Plasma HIV-1 RNA data will be monitored closely as subjects enter the Maintenance Period in order to prevent subjects from continuing on a regimen if existing data indicates that they are at unacceptable risk of inadequate maintenance of virologic suppression. The number of protocol defined virologic failures during the Maintenance Period will be monitored in all subjects that have at least 4 weeks of either of the Maintenance Period IM dosing regimens (Week 4). If the number of failures meets or exceeds the thresholds specified in the table below (Table 6), this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review and possible discontinuation of that treatment arm. If an inadequate response is seen in any arm and it is determined by IDMC that that arm should be discontinued, then subjects on that treatment arm can be switched to the remaining IM arm.

Table 6 Number of protocol-defined virologic failures on Maintenance Period that constitute strong evidence of inadequate virologic response

Number of subjects that had at least four weeks of maintenance dose on IM	Number of protocol-defined virologic failures after maintenance dose on IM
3-21	>=3
22-32	>=4
33-43	>=5
44-54	>=6

Number of subjects that had at least four weeks of maintenance dose on IM	Number of protocol-defined virologic failures after maintenance dose on IM
55-65	>=7
66-75	>=8
76-86	>=9
87-97	>=10
98-100	>=11

The thresholds described in this table are derived on the basis of the ratio of the likelihoods for the null hypothesis (H_0) that there is a subgroup of subjects with inadequate maintenance of virologic suppression and the alternative hypothesis (H_1) that the only failures in the study are due to poor compliance. For this analysis, H_0 translates to a protocol defined virologic failure rate of 20% or higher (as defined in Section 4.6) and H_1 translates to an expected 3% rate of protocol defined virologic failures. For the first IDMC review, if the true rate of virologic failure is 20% as specified in H_0, the probability to detect the inadequate virologic suppression is greater than 70%. If the true rate of virologic failure is 3%, the probability that the number of virologic failures observed will exceed the threshold is less than<1%. Further details on this method are contained in the IDMC charter. Each threshold represents strong evidence in favour of H_0 over H_1 [Royall, 1997].

The scenarios described above are not exhaustive – it is possible that the overall failure rate does not meet the threshold but that a subgroup of subjects (e.g. with a given combination of mutations or fold resistance to CAB above an as yet unknown threshold) are consistently failing. GSK will monitor virologic response by Baseline genotype and may halt one or more treatment arms if at any time subjects are deemed to be at an unacceptable risk of an inadequate response on the basis of such monitoring, although the high number of possible genotypic subgroups precludes pre-specification of precise thresholds for such action.

The number of protocol defined virologic failures will also be monitored in subjects switching from oral CAB 30 mg + ABC/3TC to the optimized IM dosing regimen of their choice (Q8W or Q4W) during the Extension Period. For subjects that have at least 4 weeks of treatment with an optimized IM dosing regimen, if the number of protocol defined virologic failures meets or exceeds the thresholds specified in the table below (Table 7) prior to all subjects completing Week 160, this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review. If an inadequate response is seen in any arm and it is determined by IDMC that that arm should be discontinued, then subjects on that treatment arm can be switched to the remaining IM dosing regimens.

Table 7 Number of protocol-defined virologic failures for each Extension Period optimized IM dosing regimen that constitutes strong evidence of inadequate virologic response – Subjects switching from Maintenance oral CAB + ABC/3TC only

Number of subjects with at least four weeks of IM dosing	Number of protocol-defined virologic failures needed to trigger IDMC review
3-21	>=3
22-32	>=4
33-43	>=5
44-54	>=6

Futility Analysis after 50% of subjects complete Week 24

An interim analysis for the purpose of review by the IDMC will be performed after approximately 50% of subjects complete Week 24. A futility rule based on Bayesian posterior probability approach will be applied to assess the probability that the IM treatment arm demonstrates comparability with the oral control arm given the partial data set. Posterior probabilities of success (Prob ($p_{IM} > p_{oral} - 0.1 \mid data$)) are provided in Table 8 for a subset of possible outcomes that could occur at the interim. Those outcomes associated with a posterior probability of success <40% may trigger a comprehensive IDMC data review and possible discontinuation of that treatment arm, although all data will be taken into consideration for making this decision.

Table 8 Posterior Probability of Success[a] at the Interim Analysis Under Various Scenarios

		# Successes in IM arm (out of 45)							
		35 (78%)	36 (80%)	37 (82%)	38 (84%)	39 (87%)	40 (89%)	41 (91%)	42 (93%)
# Successes in Oral arm (out of 23)	18(78%)	0.564	0.678	0.753	0.850	0.913	0.955	0.979	0.993
	19(83%)	0.454	0.558	0.679	0.782	0.859	0.931	0.966	0.986
	20(87%)	0.346	0.465	0.574	0.694	0.805	0.890	0.942	0.974
	21(91%)	0.244	0.348	0.455	0.584	0.706	0.829	0.907	0.961
	22(96%)	0.146	0.231	0.335	0.461	0.604	0.736	0.845	0.926
	23(100%)	0.081	0.135	0.218	0.324	0.473	0.612	0.755	0.874

a. Posterior probability of success is defined as (prob($p_{IM} > p_{oral} - 0.1 \mid data$)) with informative prior Beta (23,2) for oral arm and non-informative prior Beta (1,1) for IM arm.

b. Highlighted cells represent outcomes with posterior probability <0.4 that may trigger a comprehensive IDMC data review.

The proposed futility analysis has 91% chance to stop the study at the interim analysis if the true response rates are 92% and 72% for the oral arm and IM arm, respectively. The power to stop the study is 46% if the true response rates are 92% and 82% for the oral arm and IM arm, respectively. The chance of stopping the study by error is 2% if the true response rates are 92% for both the oral arm and IM arm.

8.3.4.3. Day 1 Interim Analysis

A Day 1 interim analysis may be conducted to support regulatory submissions and/or scientific conference presentations once the last randomized subject has completed the Day 1 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to evaluate efficacy, safety and tolerability of CAB 30 mg once daily plus ABC/3TC once daily in the Induction Period. Only data from the Induction Period would be summarized in this analysis.

8.3.4.4. Week 32 Primary Analysis

The Week 32 primary analysis will be conducted once the last randomized subject has completed the Week 32 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of both IM dosing regimens of CAB LA + RPV LA and to select a regimen for further development should both IM dosing regimens be comparable to the oral control arm.

8.3.4.5. Week 48 Analysis

The Week 48 analysis will be conducted once the last randomized subject has completed the Week 48 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the safety, tolerability and durability of antiviral response of both IM dosing regimens of CAB LA + CAB LA and to confirm the selected regimen for further development should both IM dosing regimens be comparable to the oral control arm.

8.3.4.6. Week 96 Analysis

The Week 96 analysis will be conducted once the last randomized subject has completed the Week 96 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to fully characterise the long term safety and efficacy profile of both IM dosing regimens of CAB LA and RPV LA.

8.3.4.7. Week 128 Extension Switch Analysis

The Week 128 analysis will be conducted once the last randomized subject has completed the Week 128 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the efficacy, tolerability, and safety of optimized IM dosing regimens for subjects switching from the oral regimen therapy at the end of the Maintenace Period.

8.3.4.8. Week 160 Analysis

The Week 160 analysis will be conducted once the last randomized subject has completed the Week 160 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the following: (a) the long-term safety and efficacy profile of both IM dosing regimens for subjects who

continued randomized IM dosing in the Extension Period and (b) the safety, tolerability and durability of antiviral response of the optimized IM dosing regimens for subjects switching from the oral regimen therapy at the end of the Maintenace Period.

Follow-up analyses after the Week 160 analysis may be conducted to more fully characterize the long-term safety and efficacy profile of CAB LA + RPV LA dosing regimens.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

All efficacy analyses, except as stated otherwise, will be based on the ITT-ME population.

The primary efficacy analysis will be based on the MSDF approach mentioned in Section 8.3.2. For the MSDF analysis, any switches in background ART after HIV-1 RNA has been collected may be considered as failures even if the switch was done to manage intolerance issues. Plasma HIV-1 RNA will be $\log_{10}$-transformed prior to statistical analyses. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be included in the derivation of the time to protocol defined virologic failure, but summary tables using OC datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any deviations from the planned analyses described in this protocol or the RAP will be detailed in the clinical study report (CSR).

For the analysis of CAB LA+RPV LA arms (IM arms) response rate relative to CAB 30 mg + ABC/3TC (oral arm), let:

X_{LA} = number of responder in IM arm, and

X_{oral} = number of responder in oral arm

The binomial distribution is the assumed likelihood of the response data, as follows:

$X_{LA} \sim$ Binomial (90, p_{IM})

$X_{oral} \sim$ Binomial (45, p_{oral})

Since the true response rate is unknown, prior distributions are placed on these parameters of interest to reflect current beliefs and balanced with acceptable decision criteria performance. Conjugate beta densities are assumed. The information pertaining to the oral arm response rate is well understood and the prior that was chosen reflects the belief that the response rate is between 78% and 99% with 95% certainty. There is very few information about the response rate for IM arm, therefore, a non-informative prior assumed.

$P_{LA} \sim$ Beta (1, 1)

$P_{oral} \sim$ Beta (23, 2)

The posterior probability that the response rate for IM arm demonstrates the comparability of oral arm is as follows:

$p_1 = P (P_{IM} > p_{oral} - 0.1 \mid data)$

A posterior probability of at least 90% (i.e., $p_1 > 0.90$) corresponds to "substantial evidence of positive outcome" and is chosen as the weight of evidence threshold.

Sensitivity analyses may be performed to assess the impact of the choice of informative prior for oral arm response rate though the analysis described above will remain primary for indication of efficacy decision-making purposes. As an alternative to the informative prior, a Beta (1, 1) prior distribution for oral arm may be considered. Full details of the planned Bayesian analyses will be provided in the RAP.

The proportion of subjects with plasma HIV-1 RNA <50 c/mL as determined by the MSDF algorithm will be provided by treatment group over the entire time on study by visit for the ITT-ME population and the ITT-E population.

In addition, an OC analysis may be performed for supportive purposes.

For the probability of comparability between two IM arms, a non-informative prior of Beta (1, 1) will be used for both IM treatment arms.

8.3.5.2. Safety Analyses

The study is designed to characterize a regimen for further evaluation on the basis of tolerability and virologic efficacy in conjunction with immunological response, safety and pharmacokinetic measures. Measures of safety and tolerability will be used to assess the regimen as detailed in the RAP of the study.

Exposure to study medication, measured by the number of weeks on study drug, will be summarized by treatment arm. The proportion of subjects reporting adverse events (AEs) will be tabulated for each treatment arm. The following summaries of AEs will be provided:

Incidence and severity of All AEs including injection site reactions;

Incidence and severity of treatment related AEs;

Incidence and severity of AEs leading to withdrawal from study;

Incidence of serious AEs (SAEs).

Laboratory data, vital signs and ECG data (absolute values and change from Baseline) will be summarized by visit and treatment group. In addition, the number and percentage of subjects with laboratory values of clinical concern will be summarized by treatment group. The proportion of subjects experiencing changes from Baseline in their National

Cholesterol Education Program (NCEP) and DAIDS lipid categories will be summarized by treatment arm.

Framingham Risk assessment will be calculated as detailed in the RAP and will be summarized by treatment arm.

8.3.5.3. Treatment Compliance

The overall proportion of IP study medication taken relative to the planned amount will be estimated via pill counts and scheduled injections and summarized by treatment arm for each IP.

8.3.5.4. Health Outcomes Analyses

Data from the eC-SSRS, HIVTSQ(s), HIVTSQ(c), and HIVMQ will be summarised by visit. Total satisfaction scores and lifestyle/ease sub-scores will be summarised at each time point by treatment group using the mean, SD, median, min and max.

In an effort to reduce 'potentially avoidable' study discontinuations (for example, lost to follow up, subject withdrawal, non-compliance, protocol violation) and to improve data quality, patient characteristics will be studied to focus retention efforts on subgroups of subjects more likely to withdraw prematurely from the study.

Further details of the analyses to be performed will be specified in the reporting and analysis plan (RAP).

8.3.5.5. Pharmacokinetic Analyses

The GSK Division of Clinical Pharmacology Modelling and Simulation (CPMS) will be responsible for the PK analysis of CAB. The Divisions of Clinical Pharmacology and Model-Based Drug Development at Janssen Research and Development will be responsible for conduct or oversight of the PK analysis for RPV.

PK analysis of the plasma CAB and RPV concentration-time data will be conducted using non-compartmental methods with WinNonlin (Version 5.2 or higher). Actual sampling and dosing times as recorded in the eCRF will be used for analysis. Predose concentration (C0) for CAB and RPV will be estimated.

Plasma CAB and RPV concentration data will be listed and summarized by week, day, and planned sampling time in both tabular and graphical forms. Plasma CAB and RPV PK parameters will be listed and summarized by CAB or RPV treatment.

Details of the PK analyses in the PK Population for CAB will be provided in the RAP.

Population PK Analysis:

A population-based PK model may be constructed based on the CAB and/or RPV PK data and individual Bayesian PK parameter estimates may be obtained, if the quality of the data permits. Data from the study could be merged with some previous data to help

the model building process. The effect of age, body size (weight, height, body surface area, and body mass index), gender, ethnic origin, HIV status, and concurrent medications (such as oral and injectable contraceptives) on CAB and/or RPV PK may be explored. Population PK analyses will be done under separate Population-PK Reporting and Analysis Plans.

8.3.5.6. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various plasma CAB and / or RPV PK parameters and pharmacodynamic measures (e.g., HIV-1 RNA, or safety measures) may be explored using simple correlation analyses or population-based PK/PD approach. Additional factors that may be considered include age, weight, BMI, gender, race, Baseline HIV-1 RNA, HIV risk factors, CDC classification, and CD4+ cell count. Details of the PK/PD analyses plans for CAB and / or RPV will be provided in separate RAPs.

8.3.5.7. Viral Genotyping/Phenotyping Analyses

The incidence of treatment emergent genotypic and phenotypic resistance to NRTIs and INIs will be summarized by treatment arm. Details of the analyses to be performed will be specified in the reporting and analysis plan (RAP).

8.3.5.8. Pharmacogenetic Analyses

See Section 11.3 for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.

Subject informed consent.

Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Section 11.3, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to

all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

The study is considered complete once all subjects have transitioned to commercially available IP, transitioned to another study for access to IP, withdrawn or completed the study per Section 3.2.

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will

meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

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11. APPENDICES

11.1. Appendix 1: CDC Classification System for HIV-1 Infections (1993)

Clinical Categories

The clinical categories of HIV infection are defined as follows:

Category A

Category A consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B (Symptomatic non-AIDS conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

Examples of conditions in clinical Category B include, **but are not limited to:**

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

Category C (AIDS indicator conditions as defined by diagnostic or presumptive measures).

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Conditions in Category C include:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration);or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent

- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV
- Non-CDC, HIV-associated conditions.

11.2. Appendix 2: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE[1]				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities[3, 4]	Symptoms causing greater than minimal interference with usual social & functional activities[3, 4]	Symptoms causing inability to perform usual social & functional activities[3, 4]	Symptoms causing inability to perform basic self-care functions[1, 2] OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of $\leq$ 2 units packed RBCs (for children $\leq$ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	$\geq$180 mmHg systolic OR $\geq$ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension		NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion		Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval					
	Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
	Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc					
	Adult > 16 years	Asymptomatic, QTc interval 0.45-0.47 sec OR Increase interval <0.03 sec above baseline	Asymptomatic, QTc interval 0.48-0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
	Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450–0.464 sec	Asymptomatic, QTc interval 0.465-0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism		NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)		Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)		NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤ 16 Years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) – Adult ≥ 18 years See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure – Pediatric < 18 years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care Functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70-80%	FEV1 or peak flow 50–69%	FEV1 or peak flow 25–49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care Functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

1. **Basic Self-care Functions** – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
2. **Basic Self-care Functions** – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
3. **Usual Social & Functional Activities** – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
4. **Usual Social & Functional Activities** – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)					
	Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62 – 5.23 mmol/L*	6.50 – 7.4 g/dL *4.03 – 4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
	Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 – 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 – 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
	Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
	Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 – 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
	Infant*†, ≤21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59 – 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
International Normalized Ratio of prothrombin time (INR)		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin		5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)		1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)		1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased		100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased		2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***				
Acidosis		NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low		3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase		1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis		NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low		16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)					
	Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
	Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
	Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)					
	Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
	Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low					
	Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
	Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)		NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin T (cTnT)		NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)					
	Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
	Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase		3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine		1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high					
	Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
	Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low					
	Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
	Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate		ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid		7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***				
Hematuria (microscopic)		6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random Collection		1 +	2 – 3 +	4 +	NA

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Proteinuria, 24 hour collection					
	Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
	Pediatric > 3 mo -< 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

11.3. Appendix 3: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular *UGT1A1* gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the *UGT1A1*28* variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to GSK1265744.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to GSK1265744. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK1265744 the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~6ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK1265744 has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK1265744.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample

Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to GSK1265744. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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11.4. Appendix 4: Liver Safety Drug Restart or Rechallenge Guidelines

VSLC GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

1. **Drug rechallenge** may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternative medicine available (Table 9, Figure 17)
2. In Phase III, **drug restart** may be considered for liver events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not associated with HLA marker of liver injury, when liver chemistries improve to within 1.5xbaseline and ALT<3xULN) (Table 10, Figure 18).

Background: Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered in one month of initial injury [Andrade, 2009]. However, some drugs seldom result in recurrent liver injury or fatality.

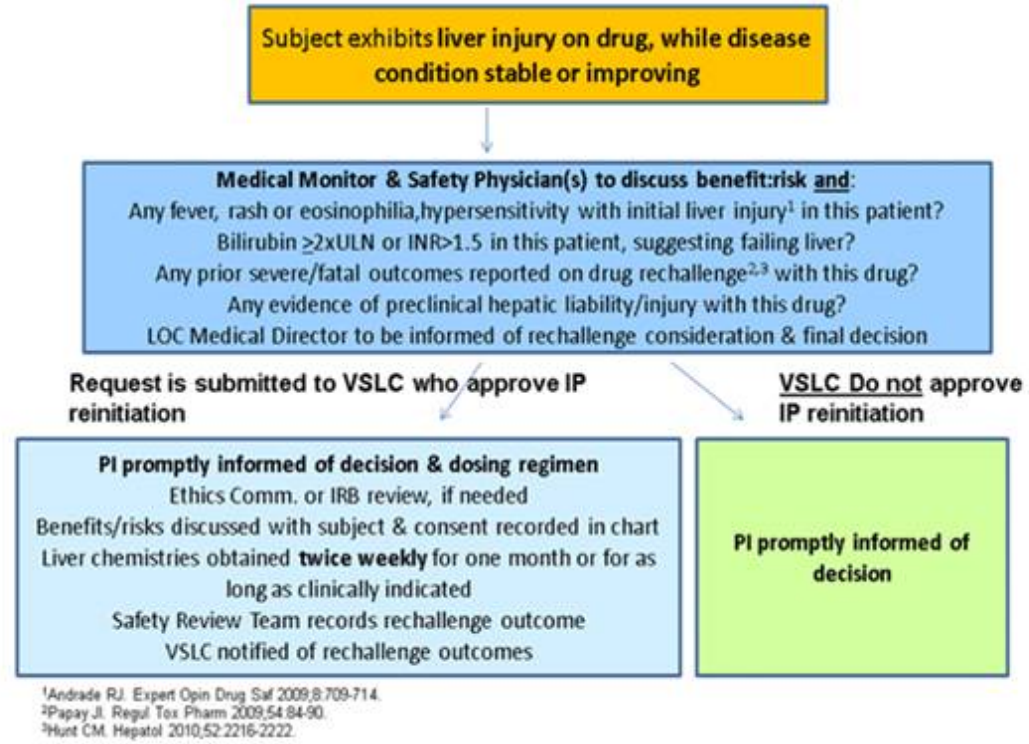
Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade 2009]
- jaundice or bilirubin≥2xULN with initial liver injury
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

VSLC Decision Process for Drug Rechallenge Approval or Disapproval (See Figure 17)

- Principal Investigator (PI) requests consideration of drug rechallenge for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment
- By definition treatment naïve subjects will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician to review the subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 9).
- The Medical Monitor and GCSP Physician are accountable to review and agree on:
  - compelling benefit of the investigational product (IP) for this subject and no alternative therapy
  - must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history
  - Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
    - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin≥2xULN (or direct bilirubin >35% of total, if available)
    - subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5
    - SAE or fatality has earlier been observed with IP rechallenge
    - IP associated with known preclinical hepatic liability/ injury
- Relevant physicians must review and agree on request for drug rechallenge:
  - Safety Team Leader, VP, or Senior Safety Physician (GSK)
  - Medicines Development Leader and Project Physician Leader (GSK)
  - Request is taken to full VSLC for final decision

Figure 17 VSLC process for drug rechallenge approval or disapproval



The local operating company (LOC) ViiV medical director (and GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.

Table 9 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin≥2xULN (direct bilirubin >35% of total)		
○ Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5		
○ SAE or fatality has earlier been observed with IP rechallenge **If yes, please provide brief explanation**:		
○ IP associated with known preclinical hepatic liability/ injury		
○ Source data defining the patients current resistance profile		
○ Previous drug history		

Drug Restart

Phase II "drug restart" can be approved by the VSLC for **transient, defined non-drug-induced liver injury if no evidence of:**

- immunoallergic injury /HLA association with injury
- DILI
- alcoholic hepatitis

Study drug held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 18):

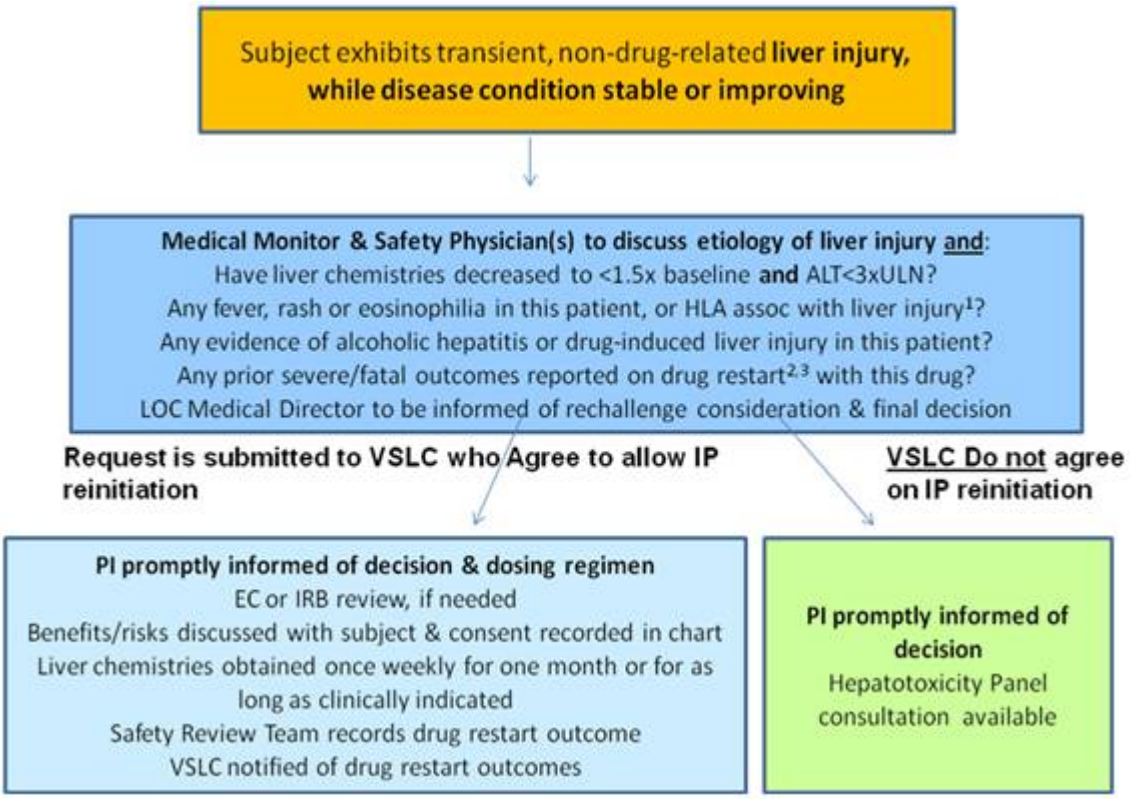
- PI requests consideration of drug re-initiation for a subject stable or improving on IP, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- GSK Medical Monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 10).
  - must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history.
- The LOC ViiV medical director (and GSK where applicable) should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.

Table 10 Checklist for Phase II drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chemistry ≤ 5x baseline & ALT<3xULN

	Yes	No
Is subject stable or improving on the investigational product (IP)?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the patients current resistance profile		
Previous drug history		

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader (GSK).
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this subject must be recorded by GCSP Physician and sent to the VSLC Secretary.
- VSLC must approve drug re-initiation and dosing regimen

Figure 18 VSLC process for drug restart approval or disapproval



1. Andrade, 2009; 2. Papay, 2009; 3. Hunt, 2010

Medical monitor, GCSP Physician and PI actions for Restart or Rechallenge following VSLC decision

Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC
- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug rechallenge (or restart) must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy (ViiV) and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain IRB/EC approval of drug rechallenge or restart, as required.
- If drug re-initiation VSLC-approved, the patient must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
  - Targeted drug rechallenge or drug restart consent form must be used.
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed twice weekly for 'rechallenge' cases and once weekly for 'restart' cases for one month or for as long as clinically indicated following drug re-initiation. If subject exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.

VSLC and the IRB/EC must be informed of the patient's outcome following drug rechallenge or restart.

Rechallenge/restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

REFERENCES:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

11.5. Appendix 5: Country Specific Requirements

No country-specific requirements exist.

11.6. Appendix 6: Changes to the Protocol

Amendment 1

Amendment 1 was finalized 28 October 2013 and applied to all countries, however, was never implemented due to a design change requiring a second amendment.

Amendment 1 was prepared to address the following changes: universal changes to naming conventions for the long acting formulation of GSK1265744, simplifying the protocol summary to allow better understanding of the protocol, clarifying the study schematic to increase understanding, clarification the purpose of and analyses to be performed by the IDMC to reflect current plans, clarification of the intent of the Day 1 analysis as a possible analysis if needed, clarification to study treatments including the addition of the ingredients of the long acting formulations of both study treatments, clarification of health outcomes objectives, timings and questionnaires, adding the assessment of exercises habits and intravenous drug use, removing some assessments to simplify study visits, updates and simplification to the time and events tables and additional miscellaneous clarifications.

General

Universal changes were made to the naming convention of the injectable formulation of GSK1265744. This was changed from GSK744 LAP to GSK744 LA and is further identified as the long acting injectable formulation. In addition, throughout the document, the term parenteral was removed therefore any abbreviations of long acting parenteral "LAP" were revised to long acting "LA". Reference to a "parenteral" regimen was revised to an "IM" regimen.

Any reference to "control regimen" or "control arm" was revised to "oral regimen" or "oral arm". Any reference to a "monthly" regimen was revised to an "every 4 weeks" regimen.

The "chronology" on the first page of the Amendment clarifies the rationale for multiple "Document Generator Numbers" or DNG numbers. For example, this is Amendment 1, but the DNG number assigned to the final version of Amendment 1 is 2013N168152_03.

Abbreviations

Addition of several abbreviations:

HIVTSQc	HIV Treatment Satisfaction Questionnaire change version
HIVTSQs	HIV Treatment Satisfaction Questionnaire status version
HIVMQ	HIV medication questionnaire
LA	Long acting

Trademarks

Added "Truvada" as a Trademark not owned by ViiV Healthcare.

Protocol Summary

This section was revised to include only key pieces of the protocol to allow the reader to better understand the protocol at a glance. Removed background, study rationale and secondary study objectives and added notable eligibility criteria, key study assessments, permitted study treatment substitutions and the definition of virologic failure.

References to Investigator's Brochures

Throughout the document, any reference to the Investigator's Brochure for either GSK1265744 or TMC278 were updated to the newest version dates 2013 and 2012 respectively.

Study Rationale, Induction Period, 4th sentence, Section 1.8

Revised to (changes struck through and underlined):

Virologic suppression in the LAI116482 study was rapid, with 83~~7~~% of GSK744 30 mg treated subjects achieving an HIV-1 RNA <50 c/mL by Week 8 suggesting that the majority of subjects in the 200056 study will be virologically suppressed for at least 8 weeks on the 16 week induction arm and for at least 16 weeks on the 24 week induction arm, prior to randomization into the Maintenance Period.

Study Rationale, Maintenance Period, 1st sentence, Section 1.8 - clarification

Revised to (changes struck through and underlined):

~~Subjects must achieve an undetectable HIV-1 RNA (<50 c/mL) at Week (-4) in order to be eligible to enter the Maintenance Period.~~ Subjects with an undetectable HIV-1 RNA (≤50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period.

Study Rationale, Extension Period, 2nd and last sentence, Section 1.8 - clarification

Revised to (changes struck through and underlined):

These subjects will also have their regimen modified at Week 96 by adding RPV 25 mg orally once daily for ~~14 days~~2 weeks.

These switch subjects ~~must achieve~~with an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit will ~~in order to~~ be eligible to enter the Extension Period.

Dose Rationale, 3rd paragraph and last paragraph, Section 1.9.1 - clarification

The 3rd paragraph was bulleted for better readability.

Revised to (changes struck through and underlined):

The preferred ~~maximum~~ IM injection volume of 2 mL using a 200 mg/mL GSK744 LA nanosuspension formulation would limit~~s the maximum~~ a single injection to 400 mg IM.

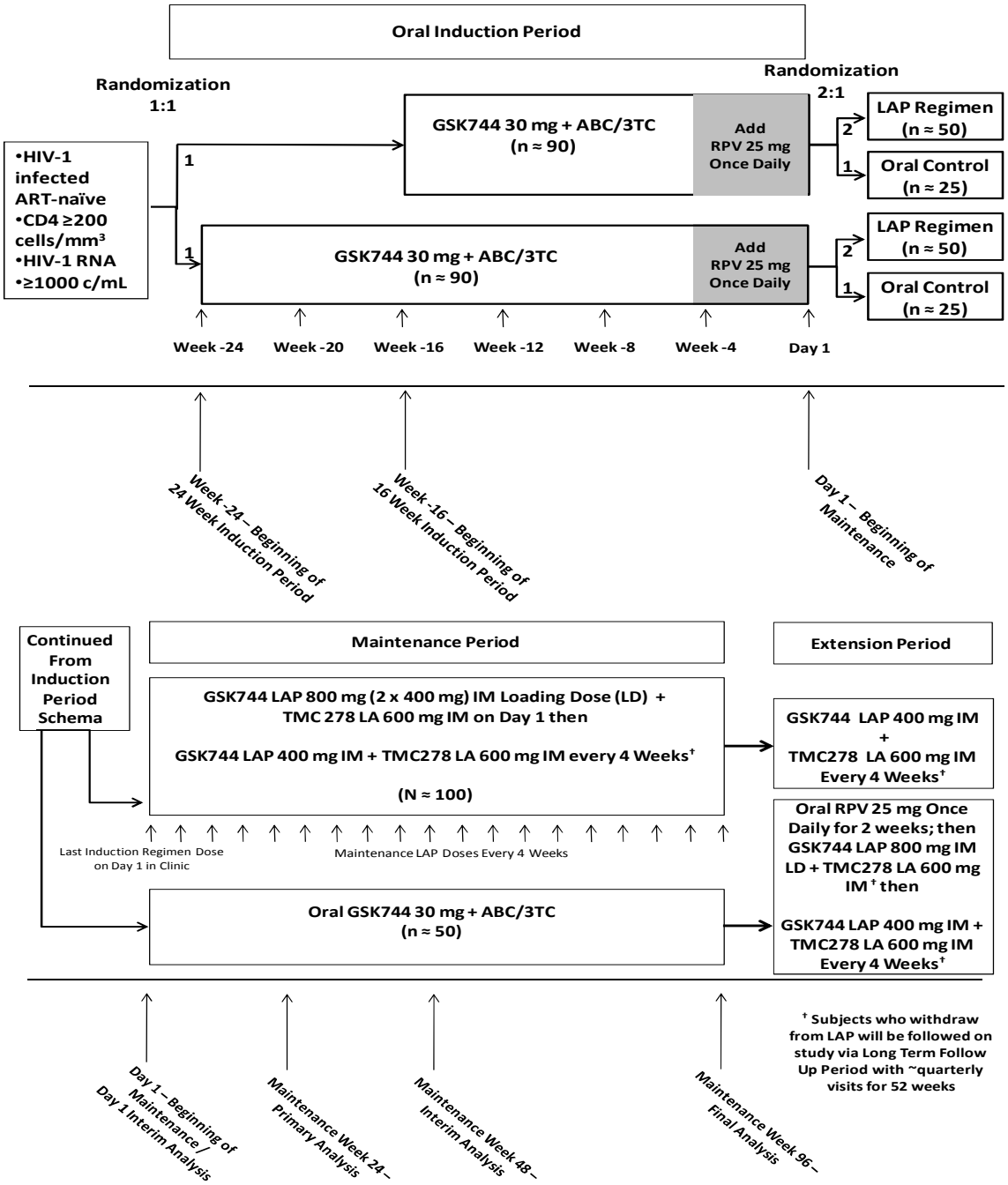
Study Objectives, Section 2 - addition

Revised to (changes struck through and underlined):

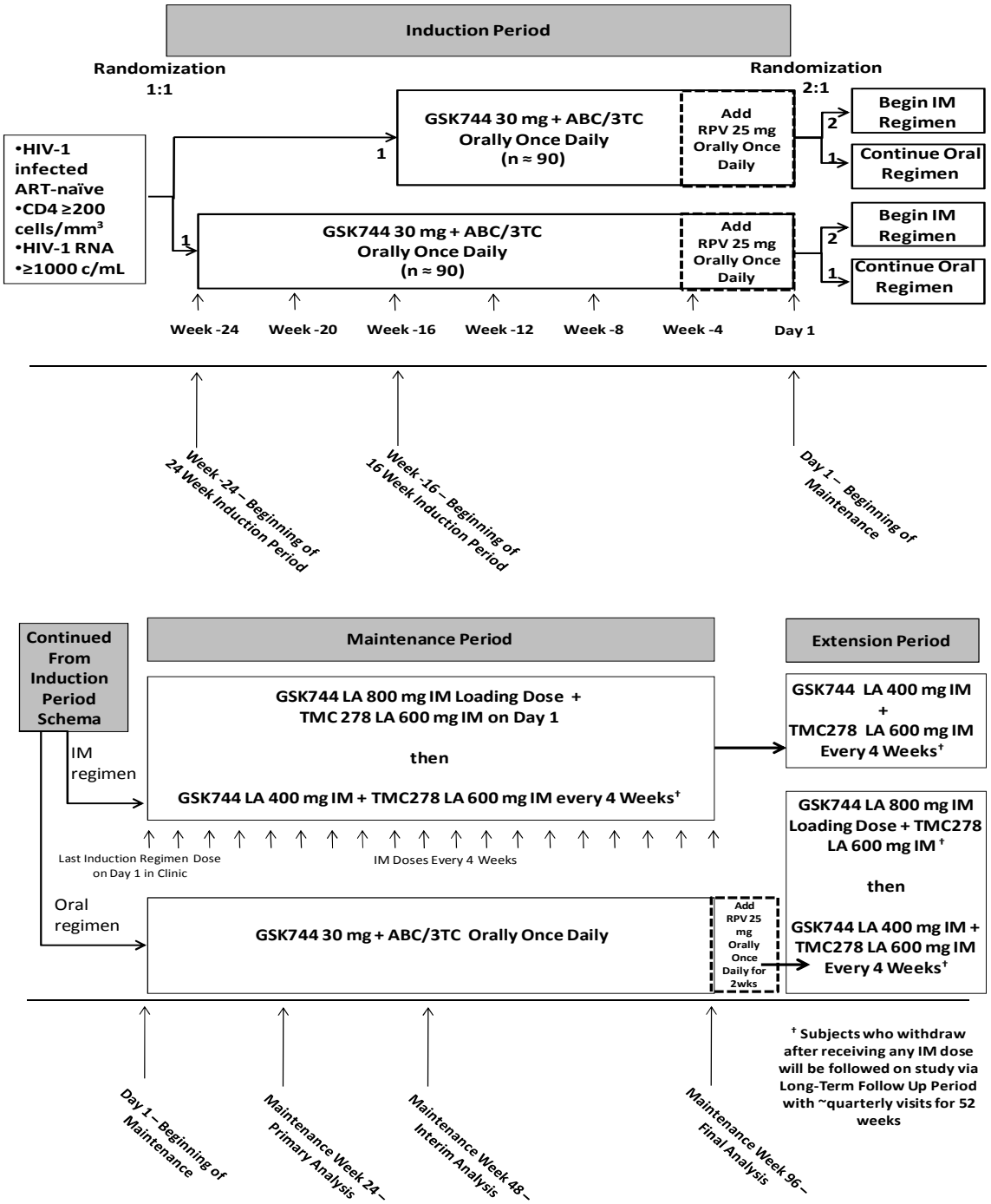
~~To evaluate the change in treatment satisfaction for subjects in the long-acting and oral regimens through Week 96 of the Maintenance Period.~~ To evaluate the treatment satisfaction for subjects on the long-acting injectable regimen with those on the oral regimen through Week 96 of the Maintenance Period.	~~Change from Baseline in treatment satisfaction for the LAP and oral regimens at Maintenance Weeks 24, 48 and 96.~~ Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time.
To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 24 of the Maintenance Period.	Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time.
To evaluate medication adherence over time.	Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.

Study Schematic, Section 3.1 - clarification

Revised from



To


Induction Period
Randomization 1:1
Randomization 2:1
•HIV-1 infected ART-naïve
•CD4 ≥200 cells/mm³
•HIV-1 RNA
•≥1000 c/mL
GSK744 30 mg + ABC/3TC Orally Once Daily (n ≈ 90)
Add RPV 25 mg Orally Once Daily
Begin IM Regimen
Continue Oral Regimen
GSK744 30 mg + ABC/3TC Orally Once Daily (n ≈ 90)
Add RPV 25 mg Orally Once Daily
Begin IM Regimen
Continue Oral Regimen
Week -24
Week -20
Week -16
Week -12
Week -8
Week -4
Day 1
Week -24 – Beginning of 24 Week Induction Period
Week -16 – Beginning of 16 Week Induction Period
Day 1 – Beginning of Maintenance
Continued From Induction Period Schema
Maintenance Period
Extension Period
GSK744 LA 800 mg IM Loading Dose + TMC 278 LA 600 mg IM on Day 1
then
GSK744 LA 400 mg IM + TMC278 LA 600 mg IM every 4 Weeks†
GSK744 LA 400 mg IM + TMC278 LA 600 mg IM Every 4 Weeks†
IM regimen
Last Induction Regimen Dose on Day 1 in Clinic
IM Doses Every 4 Weeks
GSK744 LA 800 mg IM Loading Dose + TMC278 LA 600 mg IM †
then
GSK744 LA 400 mg IM + TMC278 LA 600 mg IM Every 4 Weeks†
Oral regimen
GSK744 30 mg + ABC/3TC Orally Once Daily
Add RPV 25 mg Orally Once Daily for 2wks
† Subjects who withdraw after receiving any IM dose will be followed on study via Long-Term Follow Up Period with ~quarterly visits for 52 weeks
Day 1 – Beginning of Maintenance
Maintenance Week 24 – Primary Analysis
Maintenance Week 48 – Interim Analysis
Maintenance Week 96 – Final Analysis

Induction Period, 2nd paragraph, Section 3.2.2 - clarification

Revised to (changes struck through and underlined):

Subjects first day on study treatment will be either Weeks (-24) or Weeks (-16) depending on the outcome of randomization. Further weeks of treatment throughout the Induction Period will be counted up to Day ~~0~~1 (Day 1 initiates the Maintenance Period).

Eligibility for Maintenance, 1st paragraph, Section 3.2.3 - clarification

Revised to (changes struck through and underlined):

Subjects ~~must achieve~~ with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit ~~in order to be~~ are eligible to enter the Maintenance Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week (-4) are not eligible to enter the Maintenance Period and will not be allowed a repeat to determine eligibility.

Maintenance Period, 2nd paragraph and last sentence, Section 3.2.4 - clarification

Revised to (changes struck through and underlined):

On the first day of the Maintenance Period (Day 1), subjects will receive their last dose of GSK744±ABC/3TC±RPV ~~Induction Period regimen~~ in the clinic and initiate either IM injections or be dispensed the oral regimen depending on the ~~outcome of~~ randomization arm. Add-on RPV treatment will be discontinued for all subjects after ~~the first day of Maintenance~~Day 1.

See the Time and Events Schedule Section 6.3 and Section 6.4 for more information.

Extension Period, 4th paragraph, last sentence, Section 3.2.5.2 - clarification

Revised to (changes struck through and underlined):

If eligible, subjects will be taking GSK744 + ABC/3TC + RPV ~~for the next 2 weeks~~from Week 98 to Week 100 of the Extension Period.

Independent Data Monitoring Committee, Section 3.2.8 – IDMC specifics will now be in the IDMC charter

Revised to (changes struck through and underlined):

An Independent Data Monitoring Committee (IDMC) will evaluate the efficacy, tolerability, and safety of GSK1265744 and TMC278 before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. This IDMC review may be conducted after approximately 45 subjects have reached Week 8 of the Maintenance Period, depending on IDMC agreement. The intent of this analysis is to identify any early safety or tolerability signals from the long acting regimen. Full details

of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter. ~~An Independent Data Monitoring Committee (IDMC) will evaluate the efficacy, tolerability, and safety of GSK744 and TMC278 after 45 subjects reach Week 8 of the Maintenance Period. The intent of this analysis is to identify any early safety or tolerability signals from the long-acting regimen. At the time of this analysis, it is expected that subjects will have exposure to GSK744 LAP and TMC278 LA of up to approximately 3 months in the subset of subjects in the 16 week Induction Period, and a shorter exposure in those who are in the 24 week Induction Period.~~

Primary Analysis, 1st paragraph, last sentence, Section 3.2.9 – Revised planned analyses and allowed for additional analyses as needed.

Revised to (changes struck through and underlined):

~~Additional analyses will be conducted at Day 1, Week 24, Week 48 and Week 96.~~ Planned analyses will be conducted at Week 48 and Week 96. Additional analyses, for example at Day 1, may be conducted to support internal decision making, scientific presentations or regulatory document preparation, as needed.

Number of Subjects, Section 4.1 – not needed

Removed the following sentences:

~~Approximately 150 subjects are planned to enter the Maintenance Period. The anticipated overall study withdrawal rate is approximately 30%.~~

Inclusion Criteria and Additional Eligibility Criteria, Section 4.2 and Section 4.4 – removed dates to allow for various updates that may occur over the life of the study

Removed reference to dated product labels and Investigator's Brochures.

Exclusion Criteria, criteria #22, Section 4.3 - clarification

Revised to (changes struck through and underlined):

Subjects who are HLA-B*5701 positive and unable to use an alternative NRTI backbone (subjects who are HLA-B*5701 positive may be enrolled if they use an alternative NRTI backbone that does not contain abacavir.

Withdrawal Criteria, Section 4.5 – allow for additional data collection

Added:

All subjects who discontinue prematurely from the study, irrespective of arm, will be asked for additional information to establish the reason for withdrawal.

And

- Subjects who cannot or do not wish to continue on to the Long-Term Follow Up Period (see Section 3.2.6).

TMC278 Tablet, Section 5.1.2 - clarification

Revised to (changes struck through and underlined):

RPV [Edurant Product Information, 2012) is provided by Janssen Research & Development, a division of Janssen Pharmaceuticals as 25 mg tablets that are off-white, round, biconvex, film-coated and debossed on one side with "TMC" and the other side with "25". RPV is manufactured by Janssen -Cilag S.p.A, Latina, Italy. RPV will be provided as globally ~~commercial~~marketed product, including US and the European Union, and overlabeled, packaged in bottles of 30 tablets. RPV tablets are to be stored at 25°C and protected from light.

GSK1265744 Injectable Suspension, Section 5.1.4 – additional information

Revised to (changes struck through and underlined):

GSK744 LA is manufactured by GlaxoSmithKline and is a sterile white to slightly colored suspension containing 200 mg/mL of GSK744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and aluminium seal. Each vial is for single use containing a nominal fill of 1.5 mL or 2.0 mL, and does not require dilution prior to administration. GSK744 LA injectable suspension is to be stored at up to 30°C, do not freeze.

GSK744 LA is composed of GSK1265744 free acid, polysorbate 20, polyethylene glycol 3350, mannitol, and water for injection.

TMC278 Injectable Suspension, Section 5.1.5 – additional information

Revised to (changes struck through and underlined):

TMC278 LA, also named JNJ-16150108-AAA 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, a division of Janssen Pharmaceuticals as a sterile white suspension containing 300 mg/mL of TMC278 as free base for administration by intramuscular (IM) injection. The product is packaged in a 2 mL USP Type I glass vial with a 13 mm grey stopper and aluminium seal. Each vial is for single use containing a nominal fill of 2.0 mL, and does not require dilution

prior to administration but requires refrigeration. TMC278 LA injectable suspension is to be stored 2-8°C, do not freeze, protected from light and kept in the outer package.

TMC278 LA is composed of TMC278 free base, poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, glucose monohydrate, sodium hydroxide, water for injection.

Dosage and Administration, Induction Period, Section 5.1.6 - clarification

Clarified to require only RPV to be taken with a meal.

Dosing Considerations for GSK744 LA + TMC278 LA, Section 5.1.7 – additional information

Added:

If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction.

Treatment Compliance, Section 5.5 – allow for additional data collection

Added:

Subject awareness and knowledge of these dosing instructions will be assessed by reviewing the answers to the HIVMQ as discussed in Section 6.13.

Prohibited Medications and Non-Drug Therapies, 4th sentence, Section 5.9.2 - clarification

Revised to (changes struck through and underlined):

Acetaminophen ~~is~~ cannot be used in patients with acute viral hepatitis.

Time and Events Schedule, Section 6 – clarification, simplification, additional information

In general, the following changes were made:

- Specified in top left of each table which period the table applies to (i.e. Procedures for 24 Week Induction)
- Added that rescreened subjects would be assigned a new subject number
- Changed “Medical” exam to “Physical” exam
- Added timings for ECG completion
- Changed requirement for vital signs to be assessed after 5 minutes of rest to “about” 5 minutes of rest

- Clarified "Health Outcomes Questionnaire" to actual questionnaires being completed: HIVSTQs, HIVSTQc, HIVMQ. Included timings of completion.
- Removed some unnecessary assessments: some fasting labs, some ECGs, some chemistry and hematology assessments
- Added Follow Up visit to all
- Split the Maintenance Time and Events (T&E) table in to 2 tables: 1 for the IM regimen (GSK744 LA+TMC278 LA) and 1 for the oral regimen (GSK744+ABC/3TC)
- Added the following to both the Maintenance and Extension T&E:

Dosing is expected to occur within 21-35 days from the previous dose while keeping to the subjects visit schedule projected from Day 1 of the Maintenance Period. **All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**

- Moved Week 98 to the Maintenance T&E, oral regimen
- Simplified telephone visits for subjects on the oral regimen
- Clarified the Extension T&E to be more clear and readable
- Changed pregnancy testing in Long-Term Follow Up to be serum instead of urine

Baseline Assessments, Medical History, Section 6.7.2 – allow for additional data collection

Changed "recent" illicit drug use to "history" of illicit drug use.

Added:

intravenous drug use history

Safety Assessments, Clinical Evaluations, Section 6.9.1 – allow for additional data collection

Added:

Exercise habits will be assessed for subjects on the GSK744 LA±TMC278 LA regimen.

Laboratory Assessments, Section 6.9.2 – not collected

Removed:

~~If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's CRF.~~

Health Outcomes, Section 6.13 – clarification, additional information

Revised to (changes struck through and underlined):

~~Health outcomes assessments will be conducted in all countries where translations of the instruments are available. Assessments are recommended to be administered at the beginning of the visit.~~

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) ~~Woodcock~~ [Woodcock, 2001 and Woodcock, 2006] was developed to evaluate treatments for HIV and patient satisfaction. The higher the score, the greater the improvement in treatment satisfaction as compared to the past few weeks. A smaller score represents a decline in treatment satisfaction compared to the past few weeks. The HIVTSQ items are summed up to produce a treatment satisfaction score (0 to 60) and an individual satisfaction rating for each item (0 to 6) and two subscales: general satisfaction/clinical and lifestyle/ease subscales.

This study will be using the HIVTSQ(s) (status version) and the revised HIVTSQ(c) (change version). T~~his~~hese measures ~~is specifically designed to~~will assess change in treatment satisfaction over time (in the same subjects) and compare current satisfaction with previous ~~satisfaction~~treatment satisfaction, from an earlier time point.

The HIV Medication Questionnaire (HIVMQ) was developed to assess subject reported medication adherence.

~~The HIVTSQ items are summed up to produce a treatment satisfaction score (0 to 60) and an individual satisfaction rating for each item (0 to 6) and two subscales: general satisfaction/clinical and lifestyle/ease subscales. These scores will be summarized and compared between the treatment groups in an exploratory analysis at Week (-12), Week (-4), Day 1, Week 24, Week 48, and Week 96, or withdrawal by treatment group.~~

~~In addition, subject tolerability data will be collected at Week (-12), Week (-4), Day 1, Week 24, Week 48, and Week 96. Details of the data collection methods will be detailed in the SPM.~~

~~Moreover, data will be collected evaluating subject adherence to study treatment at Week (-12), Week (-4), Day 1, Week 24, Week 48 and Week 96. Details of the data collection methods will be detailed in the SPM.~~

The HIVTSQ(s) will be administered at the following time points:

- Induction: Week -20 in the 24 Week Induction Period and Week -12 in the 16 Week Induction Period and Week (-4) (pre-dose) in both Induction Periods

- Maintenance: pre-dose at Day 1 and post-dose at Week 4, Week 8, Week 24, Week 48, Week 96 & Withdrawal

The HIVTSQ(c) will be administered at the following time points:

- Maintenance: Week 24 and at Withdrawal for subjects withdrawn between Week 4 and Week 24

HIVMQ will be administered at the following time points:

- Induction: Week (-4)

- Maintenance: Week 8, Week 24, Week 48, Week 96 & Withdrawal

    - IM Regimen: Complete post-injection

    - Oral Regimen: Preferably completed at the beginning of the visit, but may be completed at any time during the visit

Qualitative interviews with 20-30 subjects may be conducted regarding the subject's experience on the injection regimen. This would be conducted under a separate IRB/IEC approved consent. Participation in the interviews would be voluntary.

Interim and Final Analysis, Section 8.3.4 – allow for IDMC details to be listed in the charter instead of the protocol and clarification

Revised to (changes struck through and underlined):

The ITT-E population will be primary efficacy population and the safety population will be the primary safety population for all analyses. All available data will be included in all interim analyses, including data beyond the designated time point except for the Day 1 analysis, if preformed, will only include data from the Induction Period.

At the first interim analysis the IDMC will evaluate the efficacy, safety and tolerability of GSK744 to determine if the GSK744 regimen is suboptimal such that it should be discontinued before all subjects transition into the Maintenance Period of the study. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

This interim analysis schedule does not require an adjustment for multiplicity since there is no possibility of a false positive finding at any of the interim analyses conducted before Week 24, and since the Week 48 and 96 analyses will be used to further characterise the long-term safety and efficacy profile of GSK744. As no hypothesis is being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity will be performed.

~~At the first interim analysis the IDMC will evaluate the efficacy, safety and tolerability of GSK744 to determine if the GSK744 regimen or the shorter length of induction is suboptimal and should be discontinued before all subjects transition into the Maintenance Period of the study. This analysis will be performed after 45 subjects reach Week 8 of the Maintenance Period and will include all data available at that time. Full details of the analyses that will be preformed and the criteria that will be used to determine if an induction length should be discontinued will be pre-specified in the IDMC Charter.~~

~~This interim analysis schedule does not require an adjustment for multiplicity since there is no possibility of a false positive at any of the interim analyses conducted before Week 24, and since the Week 96 analysis will just be used to fully characterise the long-term safety and efficacy profile of GSK744. As no hypothesis is being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity will be performed.~~

Futility Interim Monitoring, 3rd and 4th sentence, Section 8.3.4.1 - clarification

Revised to (changes struck through and underlined):

If the number of failures meets or exceeds the thresholds specified in the table below (Table 6), this will be considered strong evidence of an inadequate response and will trigger a comprehensive <u>IDMC</u> data review and possible discontinuation of that treatment arm. If an inadequate response is seen in the shorter induction length arm and it is determined that that arm should be discontinued, then subjects on that treatment arm still in the Induction Period can~~will~~ be switched to the longer induction length.

IDMC Interim Analysis, Section 8.3.4.2 – allow for IDMC details to be listed in the IDMC charter instead of the protocol, clarification

Revised to (changes struck through and underlined):

~~The purpose of these analyses is for the Independent Data Monitoring Committee to evaluate the efficacy, safety and tolerability of GSK744 at early time points in the study. The IDMC will review at least one analysis, an analysis of all data available at the time 45 subjects reach Week 8 of the Maintenance Period. This analysis will be used to remove any sub optimal induction length from the study before all subjects transition into the Maintenance Period. As subjects enter the Maintenance Period of the study the protocol defined virologic failure rate will be continually monitored. If the number of failures meets or exceeds the thresholds specified in Table 4, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC should this occur prior to all subjects completing Week 24. The IDMC charter will contain detailed safety summaries and efficacy analyses that will be provided~~

<u>The purpose of these analyses is for the Independent Data Monitoring Committee (IDMC) to evaluate the efficacy, safety and tolerability of GSK744 at early time points in the study. The IDMC will review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. Full details of the</u>

analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter, with IDMC agreement.

As subjects enter the Maintenance Period of the study, the protocol defined virologic failure rate will be continually monitored. If the number of failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

Day 1 Interim Analysis, Section 8.3.4.3 - clarification

Revised to (changes struck through and underlined):

A Day 1 interim analysis may be conducted to support regulatory submissions and/or scientific conference presentations once the last randomized subject has completed the Day 1 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to evaluate efficacy, safety and tolerability of GSK744 30 mg once daily plus ABC/3TC once daily in the Induction Period. Only data from the Induction Period would be summarized in this analysis. ~~The Day 1 interim analysis will be conducted once the last randomized subject has completed the Day 1 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to evaluate efficacy, safety and tolerability of GSK744 30 mg once daily plus ABC/3TC once daily in the Induction Period.~~

Health Outcomes, Section 8.3.5.4 - clarification

Revised to (changes struck through and underlined):

Data from the eC-SSRS, HIVTSQ(s), HIVTSQ(c), and HIVMQ will be summarised by visit. Total satisfaction scores and lifestyle/ease sub-scores will be summarised at each time point by treatment group using the mean, SD, median, min and max.

~~Data from the C-SSRS will be summarised by visit.~~

In an effort to reduce 'potentially avoidable' study discontinuations (for example, lost to follow up, subject withdrawal, non-compliance, protocol violation) and to improve data quality, patient characteristics will be studied to focus retention efforts on subgroups of subjects more likely to withdraw prematurely from the study.

~~Each HIVTSQ item is scored 0-6 where a higher score indicates greater satisfaction with treatment. The HIVTSQ items are summed up to produce a treatment satisfaction total score (0 to 60) and a lifestyle/ease sub-score (0 to 30).~~

~~The number and proportion of subjects with each response (0-6) to each of the 10 items in the HIVTSQ will be summarised at Week (-12), Week (-4), Day 1, Week 24, Week 48 and Week 96 by treatment group. Total satisfaction scores and lifestyle/ease sub-scores~~

~~will be summarised at Week (-12), Week (-4), Day 1, Week 24, Week 48 and Week 96 by treatment group using the mean, SD, median, min and max.~~

Amendment 2

Amendment 2 applies to all countries.

Amendment 2 was prepared to introduce a major a design change. The Induction Period was consolidated into a single 20 Week arm. An additional IM dosing arm was added: GSK744 LA 600 mg IM + TMC278 LA 900 mg IM every 8 weeks (Q8W). As such, much of the protocol was amended to consolidate the Induction Period and to add a 3rd dosing arm.

Major changes include complete replacement of the protocol summary, the dose rationale was revised to support the Q8W IM dosing regimen, objectives and endpoints were updated including changing the primary endpoint from Week 24 to Week 32, updated the dosing and administration to reflect requirements for the Q8W arm, the study design and schematic updated, increased sample size to 265 subjects, all Time and Event Tables were replaced, PK sampling strategy and data analysis and statistical considerations updated.

Additionally, the liver stopping criteria and subsequent IP restarting / rechallenge information was revised and added, respectively.

Finally, the requirement to have hepatic impairment measured by Child-Pugh assessments was removed. Hepatic impairment will be assessed by multiple other means (labs and physical assessments).

General

Clarifications of naming conventions of GSK1265744 and TMC278 (both formulations) were made throughout to document to be in line with the defined terms in Section 1.2. In addition, the Induction Period was revised throughout the document to be 20 weeks instead of 24 and 16 Weeks. The dosing regimen was modified to reflect two IM dosing regimens are being evaluated [every 4 weeks (Q4W) and every 8 weeks (Q8W)] and one oral dosing is being evaluated (oral). This change was made throughout the document.

Week 48 data from LAI116482 was added.

Updates to the Sponsor contact information.

Various clarifications throughout.

Abbreviations

Addition of several abbreviations:

BMI	Body Mass Index
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
PDVF	Protocol Defined Virologic Failure
PopPK	Population Pharmacokinetics
Q4W	Every 4 Weeks
Q8W	Every 8 Weeks
SVF	Suspected Virologic Failure
VSLC	ViiV Safety and Labeling Committee

Protocol Summary

This section was completely replaced to reflect the new design. Most sections were revised with the exception of key study assessments, permitted study treatment substitutions and the definition of virologic failure.

References to Investigator's Brochures and Product Information

Throughout the document, any reference to the Investigator's Brochure or product information for TMC278 was updated to the newest version dates 2013 and June 2013 (Edurant) respectively.

Section 1.4 GSK1265744 – Long Acting Injectable (GSK744 LA)

Original text:

A long acting (LA) injectable formulation of GSK1265744 (GSK744 LA) is also in development and has been dosed in over 98 HIV-1 uninfected subjects at doses between 100-800 mg with an adverse event (AE) profile similar to oral dosing of GSK744. The LA injectable formulation has been dosed intramuscularly (IM) and subcutaneously (SC), and has been generally well-tolerated. Painless nodules were more common following SC injections than IM injections. Intramuscular injection site reactions have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date. No treatment emergent serious AEs have been reported. [Preliminary data from ongoing study LAI115428 GlaxoSmithKline Document Number 2011N112455_03 and GlaxoSmithKline Document Number RM2010/00170/04: LAI114433].

All of the above characteristics make GSK744 an attractive compound for continued HIV drug development.

Revised text:

GSK744 LA, a long acting injectable formulation of GSK1265744, has been dosed in 136 healthy subjects. Subjects have received single or repeat doses of GSK744 LA at doses between 100 to 800 mg, either intramuscularly (IM) or subcutaneously (SC) and

either alone or in combination with TMC 278 LA(completed study LAI114433 [single dose LA, n=58], ongoing study LAI115428 [repeat dose LA, n=40], and ongoing study LAI116815 [single dose LA, n=38]). The adverse event (AE) profile has been similar tothose of GSK744 (oral). To date, no studies in HIV-1 infected subjects have been conducted with GSK744 LA.

GSK744 LA (has been generally well-tolerated as either an IM or SC dose. Intramuscular injection site reactions (ISRs) have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date. Erythema, nodules, induration, and warmth at the injection site were most commonly reported in healthy subjects. Painless nodules were more common following SC injections than IM injections. No treatment emergent serious AEs have been reported. [Preliminary data from ongoing study LAI115428 GlaxoSmithKline Document Number 2011N112455_03 and GlaxoSmithKline Document Number RM2010/00170/04: LAI114433].

All of the above characteristics make GSK1265744 an attractive compound for continued HIV drug development.

Section 1.5 TMC278 - Oral (RPV)

Revised to (changes struck through and underlined).

RPV, the oral formulation of TMC278 (~~rilpivirine, RPV~~Edurant), is a diarylpyrimidine derivative~~, is~~and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. RPV~~, and~~ is currently approved as a 25 mg oral tablet formulation in ~~for use in antiretroviral (ARV) treatment-naïve patients in the~~ multiple countries such as the US, EU and Canada for use in antiretroviral (ARV) treatment-naïve patients ~~and other countries~~ as per the approved label in each country / region.

Section 1.6 TMC278 – Long Acting Injectable (TMC278 LA)

Revised to (changes struck through and underlined).

~~Rilpivirine~~ TMC278 ~~can~~ is also ~~be~~ formulated as a long acting injectable (TMC278 LA) with PK that could support~~s~~ IM dosing every 4 or 8 ~~or more~~ weeks.

And

In C158 (N=20~~19~~) , TMC278 LA injectable suspension in the current formulation after single IM injection of 300 mg or of 600 mg, or after multiple dosing regimens of 3 successive IM doses was generally safe and well tolerated.

Added:

In LAI115428, TMC278 LA was administered as successive monthly IM injections as 1200/900 mg or 1200/600 mg along with GSK744 LA. As noted in Section 1.4, the injections were generally well tolerated, no subject discontinued due to an ISR, and no

treatment emergent serious AEs have been reported. [Preliminary data from ongoing study LAI115428 GlaxoSmithKline Document Number 2011N112455_03].

Section 1.7 - Study LAI116482

Original text:

LAI116482 is an ongoing Phase IIb dose-ranging study (GSK744 10 mg, 30 mg, 60 mg) evaluating the utility of a two-drug, two-class combination (GSK744 + RPV) when both are given as a once daily oral regimen following induction of virologic suppression using GSK744 plus 2 investigator selected NRTIs. To date, the study has enrolled 244 subjects, 181 of whom received one of three oral dose regimens of GSK744 (10 mg, 30 mg or 60 mg) plus 2 NRTIs. A Week 24 planned interim analysis is complete and demonstrated similar antiviral activity across the three dosing arms of GSK744 in combination with 2 NRTIs, which compared favourably to the control regimen of EFV 600 mg once daily plus 2 NRTIs. Rates of protocol defined virologic failure through Week 24 were low across all study arms (one subject receiving each dose of GSK744 and three subjects receiving EFV) without emergence of new genotypic or phenotypic resistance in any of these subjects.

Sixty-one percent of subjects were treated with investigator selected Truvada (tenofovir/emtricitibine, TDF/FTC) and 39% of the subjects were treated with EPZICOM/KIVEXA (abacavir/lamivudine, ABC/3TC) at randomization. Similar virologic response rates (HIV-1 RNA < 50c/mL) through 24 weeks were seen in subjects taking GSK744 + ABC/3TC (87%) and in subjects taking GSK744 + TDF/FTC (87%).

The most common treatment-emergent AEs reported for subjects on one of the GSK744 doses, were nausea, headache, and diarrhea. One subject receiving GSK744 60 mg had a Grade 3 headache. All other AEs were Grade 1 or 2 with the majority of them being Grade 1. Four subjects on GSK744 verses eight on EFV withdrew due to an AE, one receiving 30 mg (panic attack) and three receiving 60 mg (hepatitis, blood lactate dehydrogenase increased, and musculoskeletal pain). The majority of GSK744 related AEs were Grade 1 and few of those AEs led to withdrawal through Week 24 (n=4 (2%)). There have been no drug related SAEs to date.

Two of the subjects that withdrew due to AE met liver stopping criteria with an ALT>10x ULN at approximately Week 4 and Week 8 after initiating study drug. Both had pre-existing steatohepatitis and were dosed with GSK744 60 mg + ABC/3TC. Both subjects remained asymptomatic, had normal serum bilirubin levels and had resolution of the ALT values after drug discontinuation. These 2 subjects were the only Grade 3-4 ALT abnormalities to date. Overall, the rates of any graded ALT or AST abnormality were similar between GSK744 and EFV dosed subjects through Week 24: ALT: 15% and 19% respectively; AST: 18% and 15% respectively.

Based upon the results through Week 24 of the LAI116482 study, and in accordance with the pre-specified dose selection criteria, a 30 mg oral dose of GSK744 has been selected to be used in combination with ABC/3TC for induction of virologic suppression in study 200056.

These data from LAI116482 support the conduct of study 200056 by demonstrating the antiviral activity of oral GSK744 when used as part of a HAART regimen. Additionally, it is anticipated that LAI116482 will provide proof of principle for GSK744 LA + TMC278 LA as a maintenance regimen, through a demonstration of oral efficacy of GSK744 + RPV as maintenance therapy.

All subjects in the ongoing LAI116482 study have entered into the Maintenance Phase. Eligible subjects enter Maintenance at Week 24 where they begin the GSK744 + RPV regimen. All subjects will have completed 24 weeks of the maintenance regimen at the time 200056 begins, permitting a robust evaluation of the virologic efficacy of the oral two drug regimen of GSK744 and RPV, prior to the conduct of the current study. These data will be made available to Investigators.

Revised text:

LAI116482 is an ongoing Phase IIb dose-ranging study (GSK744 10 mg, 30 mg, 60 mg) evaluating the utility of a two-drug, two-class combination (GSK744 + RPV) when both are given as a once daily oral regimen following induction of virologic suppression using GSK744 plus 2 investigator selected NRTIs. Eligible subjects enter Maintenance at Week 24 where they began the GSK744 + RPV regimen.

To date, the study has enrolled 244 subjects, 181 of whom received one of three oral dose regimens of GSK744 (10 mg, 30 mg or 60 mg) plus 2 NRTIs. A planned Week 48 (24 weeks on Induction and 24 weeks on two-drug Maintenance) analysis is complete and demonstrated similar antiviral activity across the three dosing arms of GSK744 in combination with RPV, which compared favorably to the control regimen of EFV 600 mg once daily plus 2 NRTIs.

Rates of protocol defined virologic failure (PDVF) through Week 48 were low across all study arms. Three subjects receiving GSK744 (one at each dose) and three subjects receiving EFV were characterized as PDVFs during Induction. During Maintenance, two subjects receiving GSK744 (10 mg and 30 mg) and one subject receiving EFV were characterized as PDVF.

During Maintenance, treatment emergent INI (Q148R) and NNRTI (E138Q) resistance mutations were identified in one of the subjects on GSK744 (10 mg). The subject experienced suspected virologic failure (SVF) at Week 48, which was subsequently confirmed. There was no change in RPV susceptibility, and a 3.08 fold change in susceptibility to GSK744. The subject reported starting an extreme low calorie diet prior to SVF. Week 26 and Week 36 RPV pre-dose concentrations for the subject were lower than concentrations seen in the Phase III RPV studies. The subject also had lower GSK744 predose concentrations in Maintenance compared to Induction. Week 48 PK for this subject is pending. By Week 16 or at time of IP discontinuation if before Week 16, 63% of subjects were treated with Truvada (tenofovir/emtricitibine, TDF/FTC) as their background dual NRTI and 37% of the subjects were treated with EPZICOM/KIVEXA (abacavir/lamivudine, ABC/3TC). Similar virologic response rates (HIV-1 RNA < 50 c/mL) through 24 weeks were seen in subjects taking GSK744 + ABC/3TC (87%) and in subjects taking GSK744 + TDF/FTC (86%). Rates continued to be similar through

Week 48, 79% for subjects taking GSK744 + ABC/3TC and 84% in subjects taking GSK744 + TDF/FTC.

The most common treatment-emergent AEs reported for subjects on any of the GSK744 doses, were nausea, headache, and diarrhea. One subject receiving GSK744 60 mg and one subject receiving GSK744 30mg had a Grade 3 headache. The Grade 3 headache for the GSK744 60mg subject occurred very early, study day 3, while the Grade 3 headache for the GSK744 30mg subject occurred on study day 343. All other AEs were Grade 1 or 2 with the majority of them being Grade 1. Six subjects on GSK744 verses eight on EFV withdrew due to an AE, one receiving 10mg (ECG abnormal and palpitations), one receiving 30 mg (panic attack) and four receiving 60 mg (hepatitis, transaminases increased, anxiety disorder and musculoskeletal pain). The majority of GSK744 related AEs were Grade 1 and few of those AEs led to withdrawal through Week 48 (n=4 (2%)). There have been no GSK744 drug related SAEs to date.

Two of the subjects that withdrew due to AE met liver stopping criteria with an ALT>10x ULN at approximately Week 4 and Week 8 after initiating study drug. Both had pre-existing steatohepatitis and were dosed with GSK744 60 mg + ABC/3TC. Both subjects remained asymptomatic, had normal serum bilirubin levels and had resolution of the ALT values after drug discontinuation. These 2 subjects were the only Grade 3-4 ALT abnormalities to date. Overall, the rates of any graded ALT or AST abnormality were similar between GSK744 and EFV dosed subjects through Week 48: ALT: 17% and 21% respectively; AST: 20% and 18% respectively.

These data from LAI116482 support the conduct of study 200056 by demonstrating the antiviral activity of GSK744 when used initially as part of a HAART regimen to induce virologic suppression. In addition, this data confirmed antiviral activity of GSK744 + RPV as a two-drug oral Maintenance regimen and provides proof of principle for GSK744 LA + TMC278 LA as a maintenance regimen.

Based upon the results through Week 48 of the LAI116482 study, and in accordance with the pre-specified dose selection criteria at Week 24, a 30 mg oral dose of GSK744 has been selected to be used in combination with ABC/3TC for induction of virologic suppression in study 200056.

All ongoing subjects in the LAI116482 study have entered into Maintenance where they have completed 24 weeks or more of the two-drug Maintenance regimen. All subjects will have completed 48 weeks of the Maintenance regimen at the time study 200056 begins dosing any IM regimen, permitting a robust evaluation of the virologic efficacy of the oral two drug regimen of GSK744 and RPV, prior to initiating the long acting injectable regimen. These data will be made available to Investigators.

Section 1.8 – Study Rationale

Revised to (changes struck through and underlined).

<u>The overall objective of this study is to select an intramuscular dosing regimen of GSK744 LA plus TMC278 LA based on a comparison of the Week 32 antiviral activity,</u>

tolerability, and safety of two IM dosing regimens, relative to GSK744 30 mg plus ABC/3TC orally once daily ~~The overall objective of this study is to evaluate the efficacy, tolerability, and safety of GSK744 LA plus TMC278 LA when both are administered as once-monthly IM injections, following once daily GSK744 + ABC/3TC FDC~~, in HIV-1 infected antiretroviral-naïve subjects.

Induction Period

The objective of the Induction Period is to induce virologic suppression prior to the initiation of the GSK744 LA + TMC278 LA regimen. In addition, the Induction Period will evaluate the safety, tolerability and efficacy of GSK744 in combination with ABC/3TC in HIV-1-infected, ART-naive adults. The Induction Period consists of an evaluation of GSK744 30 mg once daily plus ABC/3TC through 20~~16~~ weeks ~~or 24 weeks. The varied length of induction, 16 weeks or 24 weeks, will help establish whether the length of time a subject remains virologically suppressed (HIV-1 RNA <50 c/mL) prior to initiating GSK744 LA + TMC278 LA treatment, impacts virologic response during the Maintenance Period.~~ Virologic suppression in the LAI116482 study was rapid, with 83% of GSK744 30 mg treated subjects achieving an HIV-1 RNA <50 c/mL by Week 8 suggesting that the majority of subjects in the 200056 study will be virologically suppressed for at least 12~~8~~ weeks ~~on the 16 week induction arm and for at least 16 weeks on the 24 week induction arm,~~ prior to randomization into the Maintenance Period. A review of the virology data from LAI116482 suggests that few subjects required greater than 16 weeks of therapy to achieve virologic suppression (HIV-1 RNA <50 c/mL), including subjects who entered the study with HIV-1 RNA >100,000 c/mL.

~~Subjects will be randomized at study entry to either the 16 or 24 week Induction Period and a difference in virologic response rates, between the two arms, is not anticipated. Initial randomization will be stratified by screening HIV-1 RNA (<100,000 or ≥100,000 c/mL).~~

Unless subjects meet a study withdrawal criterion, their regimen will be modified during Induction at Week (-4) by adding on RPV 25 mg orally once daily. RPV is being added to the ART regimen for all subjects at Week (-4) to establish safety and tolerability of RPV in individual subjects prior to initiating treatment with GSK744 LA + TMC278 LA during the Maintenance Period. Subjects who do not or cannot tolerate GSK744 or RPV during this period should not enter the Maintenance Period. At the majority of time points, the incidence of (treatment related) AEs in the Phase III RPV studies were comparable between the RPV and control group and highest during the first 4 weeks of treatment. Median time to onset of first rash events was 10.5 days. No grade 4 rash events were reported. In addition, this RPV add on will serve as a pharmacokinetic lead in, achieving steady state levels of RPV, prior to the administration of TMC278 LA [Rashbaum, 2011a and Rashbaum, 2011b].

Maintenance Period

Original text:

Subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period.

The objective of the Maintenance Period of this study is to assess the ability of a long-acting two-drug ART regimen, consisting of intramuscularly injected GSK744 LA 400 mg (following a loading dose of 800 mg) plus TMC278 LA 600 mg every 4 weeks, to maintain virologic suppression for 96 weeks with the primary endpoint at Maintenance Period Week 24. Subjects eligible to enter the Maintenance Period will enter a second randomization at Day 1 onto either the IM regimen or will remain on GSK744 (30 mg) + ABC/3TC (oral regimen). All subjects will discontinue the Induction regimen (including the add-on of RPV) after a final dose in the clinic on Day 1. Data from the Maintenance Period will be used to evaluate the ability of this long-acting two-drug ART regimen to maintain virologic suppression through Week 96 of the Maintenance Period. The second randomization period will serve to ensure an equal comparison between the two-drug long acting regimen and the oral comparator, through Week 24, Week 48 and Week 96 in virologically suppressed subjects. This well-characterized study population will permit a thorough evaluation of the ability of an investigational two-drug, long-acting injectable combination to maintain virologic suppression. While both drugs, GSK744 LA and TMC 278 LA, have been studied with both SC and IM administration, the IM administration is being progressed into study 200056 to best accommodate the required injection volumes of both drugs and the better tolerability of TMC278 LA IM, relative to SC.

The selection of GSK744 30 mg + ABC/3TC as an oral comparator regimen in this study, will allow for a direct comparison of subjects who either i) continue their existing regimen or ii) simplify their regimen to a once monthly long-acting regimen. The chosen comparator will also allow for a direct comparison of oral daily pill taking vs. every 4 week IM administration, as it relates to efficacy, tolerability, safety, and acceptability. Normalizing the comparator populations through a second randomization at Day 1, will also serve to strengthen this comparison.

Long-term maintenance of HIV virologic suppression will be assessed.

Revised text:

All subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period.

The objective of the Maintenance Period of this study is to assess the ability of a two-drug regimen of GSK744 LA and TMC278 LA to maintain virologic suppression for 96 weeks with the primary endpoint occurring after 32 weeks. Two injectable IM dosing regimens (Q8W and Q4W) and one oral control dosing regimen will be evaluated.

Subjects eligible to enter the Maintenance Period will be randomized 2:2:1 at Day 1 to one of the dosing regimens described below:

- GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)
    - + Loading Dose of GSK744 800 mg at Day 1

  - + Loading Dose of GSK744 600 mg at Week 4

- GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)
  - + Loading Dose of GSK744 800 mg at Day 1
- GSK744 30 mg + ABC/3TC once daily

Randomization will be stratified by HIV-1 RNA <50 c/mL before Week (-8) (yes or no).

All subjects on either IM regimen will discontinue the Induction regimen (including the add-on of RPV) after a final dose in the clinic on Day 1. Subjects on the oral regimen will discontinue the add-on of RPV after a final dose in the clinic on Day 1.

While both drugs, GSK744 LA and TMC 278 LA, have been studied with both SC and IM administration, the IM administration is being progressed into study 200056 to best accommodate the required injection volumes of both drugs and to ensure good tolerability.

The selection of GSK744 30 mg + ABC/3TC as an oral comparator regimen in this study, will allow for a direct comparison of subjects who either i) continue their existing regimen or ii) simplify their regimen to one of the IM regimens. The chosen comparator will also allow for a direct comparison of oral daily pill taking vs. Q4W and Q8W IM administration, as it relates to efficacy, tolerability, safety, and acceptability. Normalizing the comparator populations byrandomizing only suppressed subjects at Day 1, will also serve to strengthen this comparison.

Long-term maintenance of HIV virologic suppression will be assessed.

Extension Period

Original text:

The Extension Period of this study will allow for a collection of longer term efficacy and safety and tolerability data from subjects receiving GSK744 LA and TMC278 LA.

Unless subjects meet a study withdrawal criterion, subjects on the oral regimen may elect to continue on the Extension Period via switching to the GSK744 LA + TMC278 LA regimen. These subjects will also have their regimen modified at Week 96 by adding RPV 25 mg orally once daily for 2 weeks. This short RPV add on will allow eligible subjects to achieve steady state levels of RPV, prior to the administration of the GSK744 LA + TMC278 LA regimen. These switch subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit will be eligible to enter the Extension Period.

Revised text:

The Extension Period of this study will allow for a collection of longer term efficacy and safety and tolerability data from subjects receiving GSK744 LA and TMC278 LA. Only

one IM dosing regimen, either Q4W or Q8W, will be taken into the Extension Period of the study [based on criteria described in the Reporting and Analysis Plan (RAP)].

Unless subjects meet a study withdrawal criterion, subjects on the oral regimen may elect to continue on the Extension Period by switching to the selected GSK744 LA + TMC278 LA dosing regimen. If eligible, their regimen will be modified prior to entering Extension by adding RPV 25 mg orally once daily for 2 weeks. This short RPV add on will allow eligible subjects to achieve steady state levels of RPV, prior to the administration of the GSK744 LA + TMC278 LA.

Long-Term Follow-Up Period

Original text:

Subjects who have received at least one dose of GSK744 LA and/or TMC278 LA are anticipated to be at high risk for development of virologic resistance if ART is interrupted. The time period during which subjects may be at greatest risk for developing virologic resistance may be the period between when drug levels fall below therapeutic exposures and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and may be dependent upon effective concentration, inhibitory concentration and half-life. After a single 800 mg dose of GSK744 LA, concentrations may be measurable for up to 52 weeks and after a single 600 mg dose of TMC278 LA, concentrations may be measurable for up to 24 weeks.

Therefore, any subject who receives at least a single dose of GSK744 LA and/or TMC278 LA and who discontinue the GSK744 LA + TMC278 LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of GSK744 LA and/or TMC278 LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. In this study, this will be accomplished by a Long-Term Follow-Up Period.

Revised text:

Subjects who have received at least one dose of GSK744 LA and/or TMC278 LA are anticipated to be at high risk for development of virologic resistance if ART is interrupted. The time period during which subjects may be at greatest risk for developing virologic resistance may be the period between when drug levels fall below therapeutic exposures and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and may be dependent upon effective concentration, inhibitory concentration and half-life. Plasma concentrations of both drugs may be measurable for approximately 52 weeks following IM injections.

Section 1.9 – Dose Rationale

Original text:

GSK1265744 – Oral and Long Acting Injectable

The oral dosing period intended for induction of virologic suppression will also serve as a lead-in period required to confirm tolerability in each subject prior to initiating the prolonged exposure following GSK744 LA injection, which has been observed to be up to 52 weeks following a single injection in some subjects [GlaxoSmithKline Document Number RM2010/00170/04: LAI114433]. GSK744 10 mg, 30 mg and 60 mg once daily in combination with 2 NRTIs achieved undetectable HIV RNA at Week 24 in 85 to 88% of HIV infected subjects [GlaxoSmithKline Document Number 2012N134026_02: LAI116482]. Plasma exposures following these oral doses are shown in Table 1. Given the equivalent efficacy across all doses at Week 24 and the more frequent ALT elevations observed following 60 mg once daily, GSK744 30 mg once daily is the clinical dose that has been selected for the Induction Period.

During the IM dosing period intended to maintain virologic suppression, GSK744 LA 800 mg IM (split into two 2 mL, 400 mg IM injections) will be administered as a loading dose on the same day as the final oral dose to maintain GSK744 plasma concentrations above the protein adjusted 90% inhibitory concentration (PA-IC90) while prolonged absorption from the depot site begins. GSK744 LA 400 mg IM every 4 weeks starting 28 days following the loading dose was selected to approximate the plasma GSK744 concentrations of the selected oral dose of 30 mg once-daily at steady state. Following an 800 mg IM loading dose and three subsequent 400 mg IM maintenance doses administered every 4 weeks in healthy subjects (LAI115428), the geometric mean GSK744 Cτ was 3.2 μg/mL, 19-fold above the PA-IC90, whereas oral 30 mg once daily (LAI116482) achieved a geometric mean plasma C0 of 4.2μg/mL,~25-fold above the PA-IC90. Geometric mean plasma area under the curve (AUC) (0-τ) following the fourth monthly dose (third monthly 400 mg IM dose) in healthy subjects was 2362μg·h/mL (LAI115428), below the AUC (0-∞) of 2652μg·h/mL observed in healthy subjects receiving a single dose of 400 mg IM in another study (LAI114433), suggesting that accumulation may be ongoing and steady state concentrations may be higher than observed after four monthly doses.

Plasma exposures after administration of GSK744 LA IM every 4 weeks:

- are expected to be similar those observed in healthy subjects (geometric mean maximum plasma drug concentration [Cmax] 4.37 μg/mL and AUC(0-τ) 2652μg·h/mL (LAI115428),
- are not expected to exceed those following oral 30 mg once daily (geometric mean Cmax, steady state (ss) 4.20 μg/mL and 28*AUC (0-τ), ss 3752μg·h/mL) studied in LAI116482,
- are expected to remain well-below exposures observed in the 60 mg level (geometric mean Cmax, ss 13.1 μg/mL and 28*AUC, (0-τ) ss 6384 μg·h/mL) in LAI116482 (See Table 1).

Despite a geometric mean Cτ lower than 30 mg orally once daily, Cτ values observed following 800 mg/400 mg IM in healthy subjects were ~2.4-fold higher than following 10 mg orally once daily in HIV infected subjects, which was equally efficacious to 30 mg orally once daily at 24 Weeks. Mean observed GSK744 concentration-time profile following GSK744 LA administration in healthy subjects with superposition of steady-state oral dosing is compared to simulated 10 mg and 30 mg orally every day regimens based on LAI116482 data in Figure 1.

The preferred IM injection volume of 2 mL using a 200 mg/mL GSK744 LA nanosuspension formulation would limit a single injection to 400 mg IM. As dose splitting increases the number of injections, possibly reducing patient tolerability, single injection maintenance doses are preferred. In addition, a maximum SC injection volume of 1mL using the 200 mg/mL nanosuspension would require a 4-injection loading dose and 2-injection maintenance doses, limiting the acceptability of delivery by the SC route of administration.

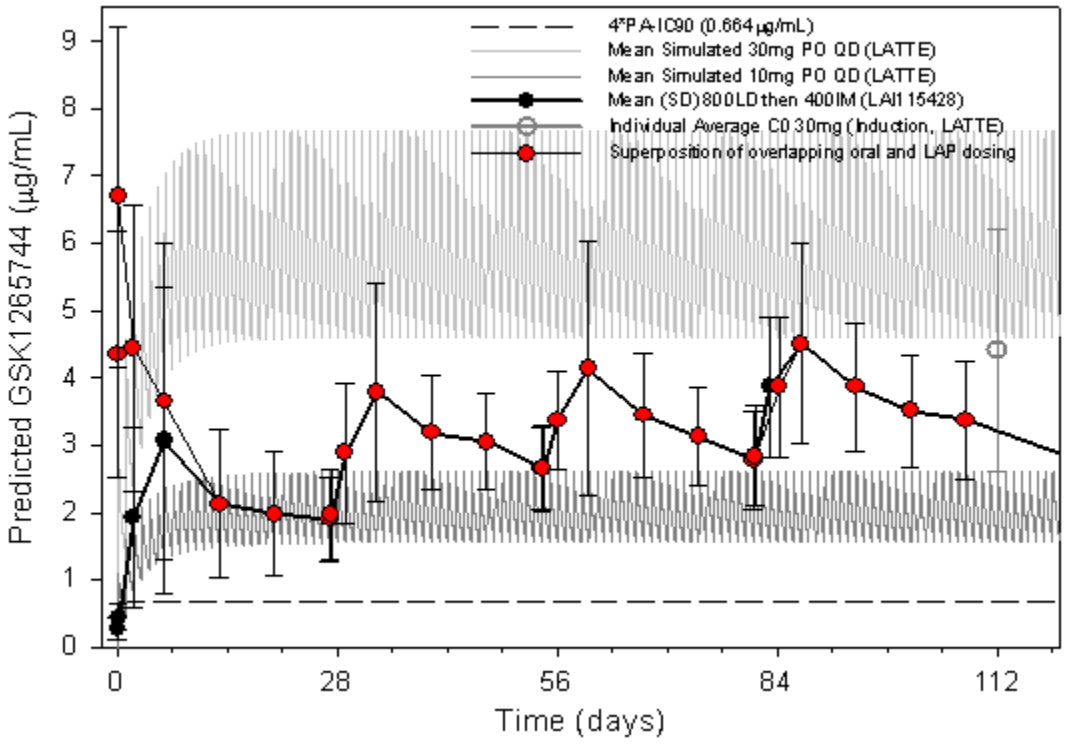
Table 1 Summary of GSK1265744 PK Parameters following oral administration in HIV infected subjects and GSK744 LA administration in healthy subjects

Route Study Population	GSK1265744 Regimen	GSK1265744 PK Parameter			
		Cτ or C0 (μg/mL)[1]	Cmax (μg/mL)[2]	AUC(0-τ) (μg• h/mL)[3]	IQ (C0:IC90 ratio)[4]
Oral LAI116482 HIV	10 mg orally every day	1.35 [45%]	2.77 [33%]	45.7 [32%]	8.13
	30 mg orally every day	4.20 [40%]	7.49 [28%]	134 [32%]	25.3
	60 mg orally every day	7.93 [39%]	13.1 [44%]	228 [57%]	47.8
IM LAI115428 HVs	800 mg IM Loading Dose/ 400 mg IM q4wk x3	3.22 [28%]	4.37 [33%]	2362 [27%]	19.4

Data presented as Geometric mean [CVb%], HV = Healthy Volunteers

1. C0: n= 57 (10 mg orally), 53 (30 mg orally), 55 (60 mg orally), 9 (800 mg/400 mg IM),
2. Cmax: n= 14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
3. AUC(0-τ): n= 14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
4. PA-IC90 determined in vitro 0.166μg/mL.

Figure 1 **Mean (SD) GSK1265744 Concentration-Time Profiles following 800 mg/400 mg IM LA Administration and with Superposition of Final 30 mg oral Steady State Dose at Day 0 compared to simulated 30 mg and 10 mg orally once daily**



TMC278 – Oral and Long Acting Injectable

All subjects will receive 4 weeks of RPV 25 mg daily, from Week (-4) through Day 1 to confirm tolerability in each subject prior to IM dosing with TMC278 LA. RPV will thus be co-administered with the GSK744 + ABC/3TC regimen. Data from study LAI116182 [GlaxoSmithKline Document Number 2012N134026_02: LAI116482] have demonstrated that there is no clinically relevant drug-drug interaction following repeat oral administration of GSK744 with RPV. With this RPV add-on, subjects will also have steady-state RPV plasma concentrations prior to starting TMC278 LA dosing.

During the Maintenance Period, subjects will receive IM injections of TMC278 LA 600 mg every 4 weeks. The selection of the TMC278 LA dosing regimen is based on achieving RPV plasma concentrations comparable to those observed with RPV 25 mg every day in HIV-infected patients.

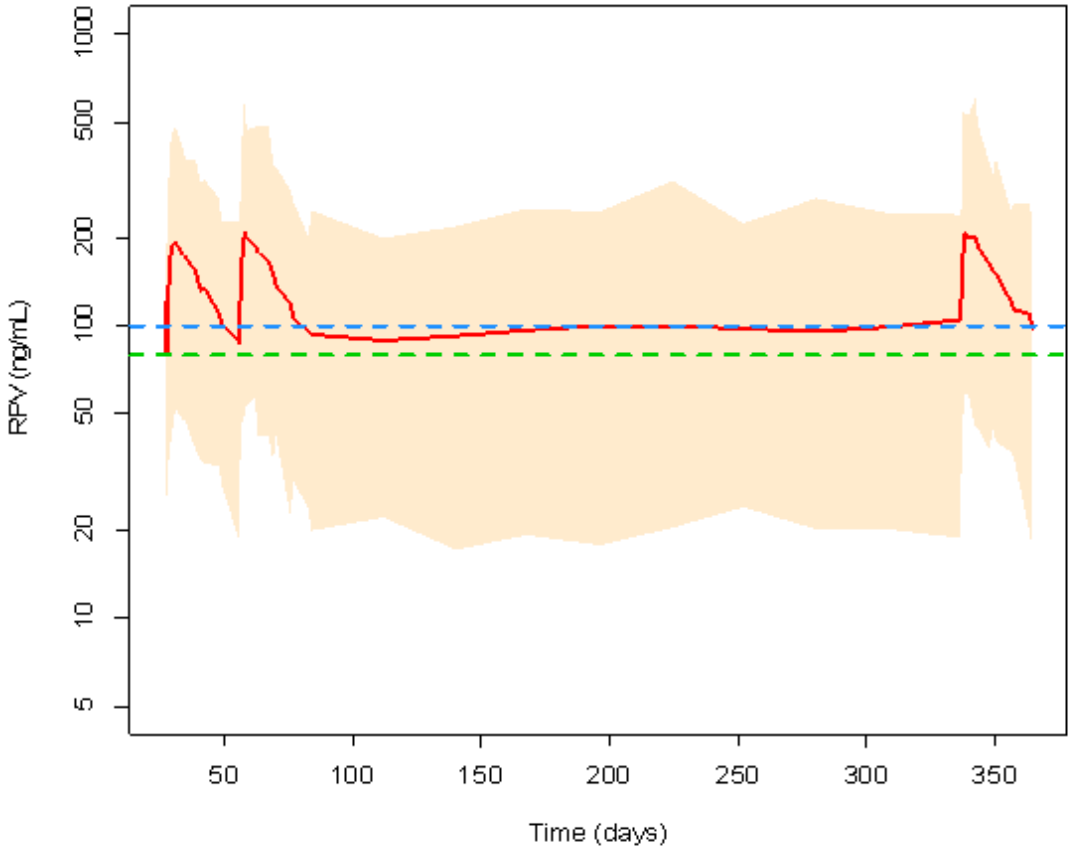
Figure 2 shows the model predicted RPV plasma concentrations with this TMC278 LA dosing regimen. The graph shows the mean profile (red curve) with the 90% prediction interval (shaded area). The curve shows a full PK profile for the first 2 injections and for the 11th injection, while for the injections in between only the trough plasma concentration (Ctrough) is shown. Figure 2 also indicates the mean PK parameters for RPV 25 mg every day in HIV-infected patients (Phase III): Ctrough of 80 ng/mL, and

Cavg (i.e., average RPV plasma concentration within a 24 hour dosing interval) of 100 ng/mL.

For the simulations, a pharmacokinetic model was used based on all available data from studies with the current TMC278 LA formulation (TMC278-C158, SSAT040, LAI115428) and the population PK model of RPV. With this model, the TMC278 LA dosing regimen (i.e., 4 weeks RPV 25 mg every day followed by IM injections every 4 weeks of TMC278 LA 600 mg) was simulated for 100 subjects. For each of these individuals, the median Ct between day 168 (i.e. after injection 5) and day 336 (i.e., after injection 11) was determined, and from these median values, the mean across subjects was calculated [GlaxoSmithKline Document Number 2011N112455_03: LAI115428].

As such, the mean steady-state Ctrough with this TMC278 LA dosing regimen is predicted to be around 95 ng/mL. This is above the mean RPV Ctrough (80 ng/mL) and close to the mean Cavg (100 ng/mL) for RPV 25 mg every day. Furthermore, as shown in Figure 2, the mean RPV plasma concentrations are already above the mean Ctrough for RPV as of the 1st injection with TMC278 LA 600 mg.

Figure 2 **Predicted Mean (90% prediction interval) RPV Plasma Concentration-Time Profile for IM injections every 4 weeks of TMC278 LA 600 mg (immediately following 4 weeks RPV 25 mg every day)**
(green dotted line represents mean Ctrough for RPV 25 mg every day; blue dotted line represents mean Cavg for RPV 25 mg every day)



Revised text:

GSK744

GSK744 10 mg, 30 mg and 60 mg oral once daily achieved similar efficacy at Week 24 of Induction when coadministered with 2 NRTIs and at Week 48 of Maintenance (24 weeks on Maintenance) when coadministered with RPV 25 mg once daily (Table 1). Rates of virologic suppression through Week 48 (Maintenance) on the two drug regimen remained similar to that attained through Week 24 (Induction) on three drug ART.

The oral dosing period intended for induction of virologic suppression also serves as a lead-in period required to confirm tolerability in each subject prior to initiating the prolonged exposure following GSK744 LA injection, which has been observed to be up to 52 weeks following a single injection in some subjects GlaxoSmithKline Document Number RM2010/00170/04: LAI114433]. Although all doses provided similar induction

and maintenance of viral suppression, GSK744 30 mg once daily was selected as the oral dose to be used in combination with ABC/3TC for induction of virologic suppression in this study. GSK744 30mg achieves higher plasma exposures than the 10mg oral dose, providing higher toxicity coverage prior to initiating IM dosing.

Based upon the results through Week 48 of the LAI116482 study, and in accordance with the pre-specified dose selection criteria at Week 24, a 30 mg oral dose of GSK744 has been selected to be used in combination with ABC/3TC for induction of virologic suppression in this study.

GSK744 LA

GSK744 10 mg, 30 mg and 60 mg orally once daily achieved similar efficacy at Week 24 of Induction when coadministered with 2 NRTIs and at Week 48 of Maintenance (24 weeks on Maintenance) when coadministered with RPV 25 mg once daily (Table 1). Rates of virologic suppression through Week 48 (Maintenance) on the two drug regimen remained similar to that attained through Week 24 (Induction) on three drug ART. The similar efficacy in all three treatment arms in LAI116482 suggests that maintaining target Cτ following IM administration of GSK744 LA with TMC278 LA at approximately the level of the 10 mg oral dose (geometric mean 1.35 μg/mL, 8.1-fold above PA-IC_{90}) should also maintain suppression of HIV infection. Once safety and tolerability are confirmed with oral dosing, maintaining target Cτ following IM administration of GSK744 LA with TMC278 LA at approximately the level of the 10 mg oral dose (geometric mean 1.35 μg/mL, 8.1-fold above PA-IC90) should be sufficient to maintain suppression of HIV infection. Maintaining a target at approximately the level of the 30 mg oral dose is not needed in Maintenance, as viral suppression and short-term tolerability have been established during Induction.

Using population pharmacokinetic (PK) modelling and simulations, GSK1265744 Cτ values for several IM dosing regimens were calculated and two regimens were selected based upon:

- ability to reach target concentration early in treatment,
- ability to maintain mean Cτ above that obtained with oral GSK744 10 mg once daily during treatment (GSK744 trough concentrations ≥1.35 μg/mL), and
- minimizing the total number of injections per visit.

Table 1 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-E Population)

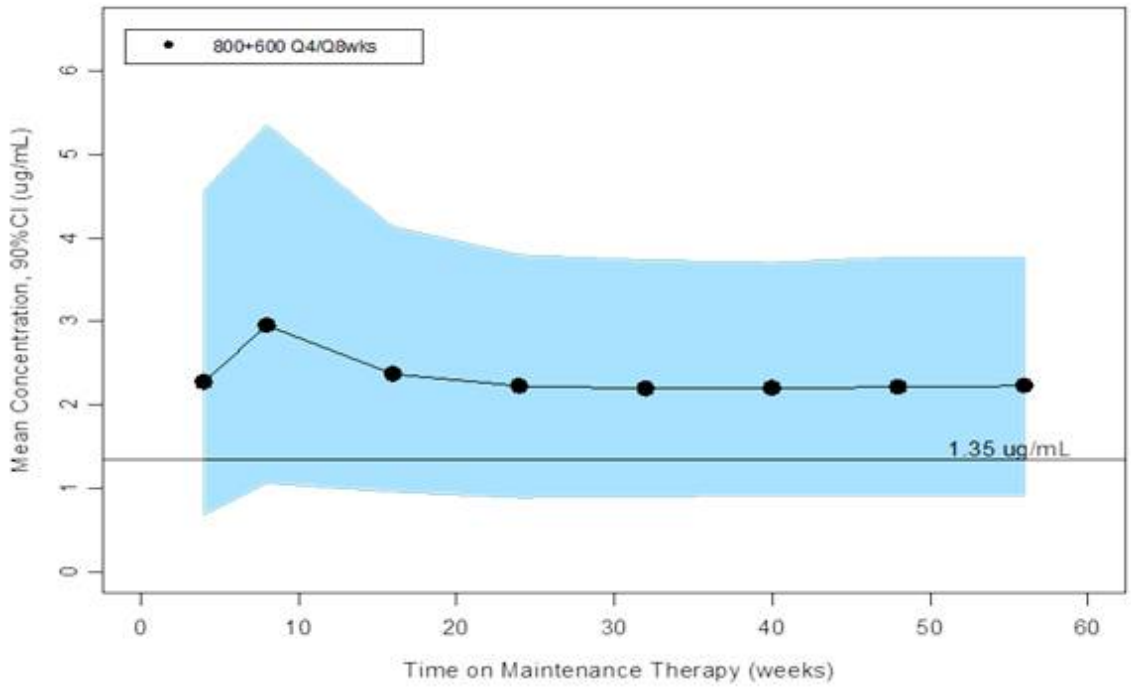
Visit	GSK744 10 mg N=60 n (%)	GSK744 30 mg N=60 n (%)	GSK744 60 mg N=61 n (%)	GSK744 Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Week 16 – Induction	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
Week 24 – Induction	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
Week 48 - Maintenance	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)

GSK744 LA Q8W

Subjects randomized to GSK744 LA Q8W will receive a GSK744 800 mg IM Loading Dose on Day 1 (within 2 hours of final oral dosing), a 600 mg IM Second Loading Dose at Week 4, and 600 mg IM Q8W starting at Week 8.

The first 800 mg IM loading dose and second 600 mg IM loading dose were selected so that ≥80% of subjects will be above 1.35 μg/mL throughout treatment. Mean (90% CI) simulated GSK744 Cτ values versus time across doses for GSK744 LA Q8W are presented graphically in Figure 1.

Figure 1 Simulated Mean (90% CI) GSK744 Trough Concentrations versus Time for GSK744 LA Q8W



At Week 56 (approximately one year of dosing), GSK744 LA Q8W is predicted to achieve GSK744 trough concentrations ≥1.35 µg/mL (target) in 84% of subjects. Although the lower bound of the 90% CI falls below 1.35 µg/mL, Cτ for all subjects remains above 4•PA-IC_{90} (0.166 µg/mL). At Week 56, geometric mean GSK744 Cτ for GSK744 LA Q8W is predicted to be 2.02 µg/mL, 1.5-fold above target and 12.2-fold above PA-IC_{90} (Table 2).

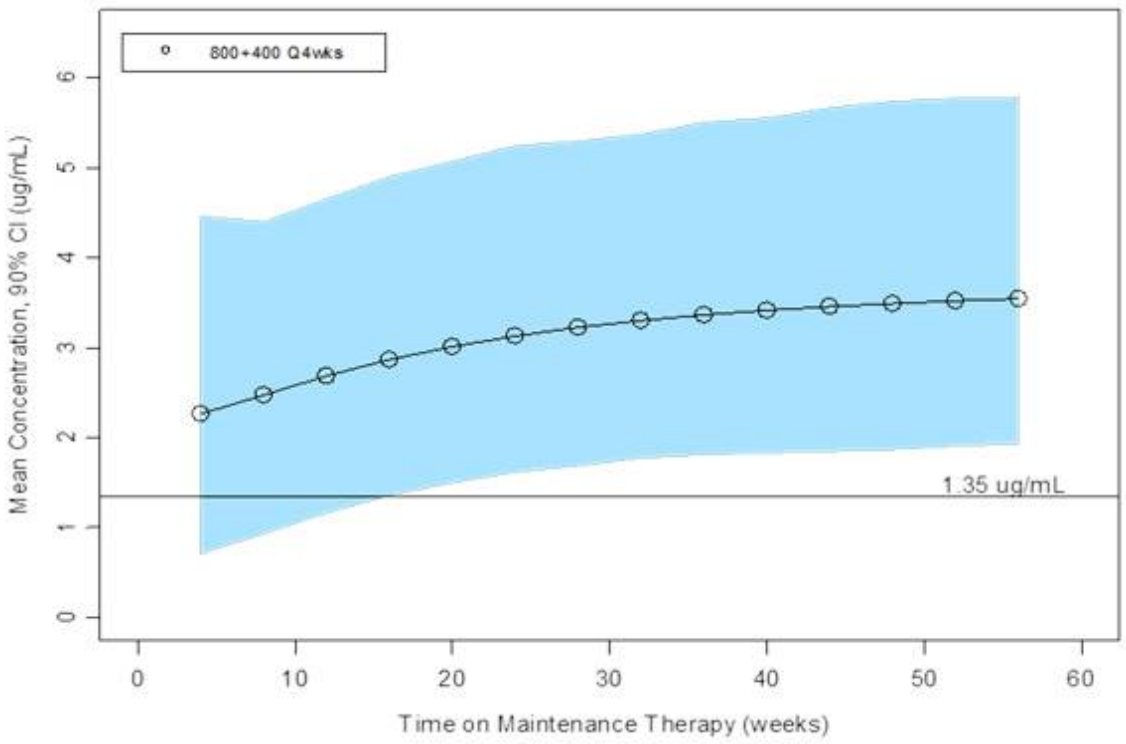
A one week delay in dosing at steady state the Q8W regimen is predicted to result in a geometric mean Cτ that is 9% lower than for dosing that is administered on schedule while remaining above the 1.35 µg/mL target associated with the 10mg oral dose.

GSK744 LA Q4W

Subjects randomized to the Q4W dosing arm will first receive GSK744 800 mg IM as a loading dose on Day 1 (within 2 hours of final oral dosing) and then, starting at Week 4, will receive GSK744 400 mg IM Q4W.

The 800 mg loading dose was selected so that ≥80% of subjects will be above 1.35 µg/mL throughout treatment, including the end of the first dosing interval. Mean (90% CI) simulated GSK744 Cτ values versus time across Q4W doses for GSK744 LA are presented graphically in Figure 2.

Figure 2 Simulated Mean (90% CI) GSK744 Trough Concentrations versus Time for GSK744 LA Q4W



At Week 56 (approximately one year of dosing), GSK744 LA Q4W is predicted to achieve GSK744 trough concentrations ≥1.35 μg/mL (target) in 99.6% of subjects. Geometric mean GSK744 Cτ for GSK744 LA Q4W at Week 56 is predicted to be 3.35 μg/mL, 2.5-fold above target, 20.2-fold above the PA-IC_{90} (0.166 μg/mL), and similar to the observed mean Cτ after 16 weeks of this regimen in healthy subjects (Table 2).

A one week delay in dosing at steady state for the Q4W regimen is predicted to result in a geometric mean Cτ that is 8% lower than for dosing that is administered on schedule while remaining above the 1.35μg/mL target associated with the 10 mg oral dose.

Table 2 Summary of GSK744 PK Parameters following oral administration in HIV infected subjects, GSK744 LA administration in healthy subjects, and following Simulations

Route Study Population	GSK1265744 Regimen	GSK1265744 PK Parameter			
		Cτ or C0 (μg/mL)[a]	Cmax (μg/mL)[b]	AUC(0-τ) (μg● h/mL)[c]	IQ (C0:IC_{90} ratio)[d]
Oral LAI116482 HIV	10 mg orally every day	1.35 [45%]	2.77 [33%]	45.7 [32%]	8.13
	30 mg orally every day	4.20 [40%]	7.49 [28%]	134 [32%]	25.3
	60 mg orally every day	7.93 [39%]	13.1 [44%]	195 [48%]	47.8
IM LAI115428 HVs	800 mg IM LD 400 mg IM Q4W x3	3.22 [28%]	4.37 [33%]	2362 [27%]	19.4
IM PopPK simulation HIV	LA Regimen #1 (200056): 800mg IM LD 400mg IM Q4W from W4	3.35 [35%]	ND	ND	20.2
IM PopPK simulation HIV	LA Regimen #2 (200056): 800mg IM LD 1 600mg IM LD 2 (Week 4) 600mg IM Q8W from W8	2.02 [52%]	ND	ND	12.2

Data presented as Geometric mean [CVb%], HIV = HIV infected subjects, HV = Healthy Volunteers, ND=Not determined, LD = Loading Dose

a. C0: n=57 (10 mg orally), 53 (30 mg orally), 55 (60 mg orally), 9 (800 mg/400 mg IM),
b. Cmax: n=14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
c. AUC(0-τ): n=14 (10 mg orally), 12 (30 mg orally), 11 (60 mg orally), 9 (800 mg/400 mg IM)
d. PA-IC_{90} determined in vitro 0.166 μg/mL.

RPV

All subjects will receive 4 weeks of RPV 25 mg once daily, co-administered with GSK744+ABC/3TC, from Week (-4) through Day 1 to confirm tolerability in each subject prior to possible IM dosing with TMC278 LA. Subjects switching from the oral regimen to the IM regimen in the Extension Period will receive 2 weeks of RPV 25 mg

once daily, from Week 102 through Week 104. Data from study LAI116182 [GlaxoSmithKline Document Number 2012N134026_02: LAI116482] have demonstrated that there is no clinically relevant drug-drug interaction following repeat oral administration of GSK744 with RPV. With this oral RPV add-on, subjects will also have steady-state RPV plasma concentrations prior to starting TMC278 LA dosing.

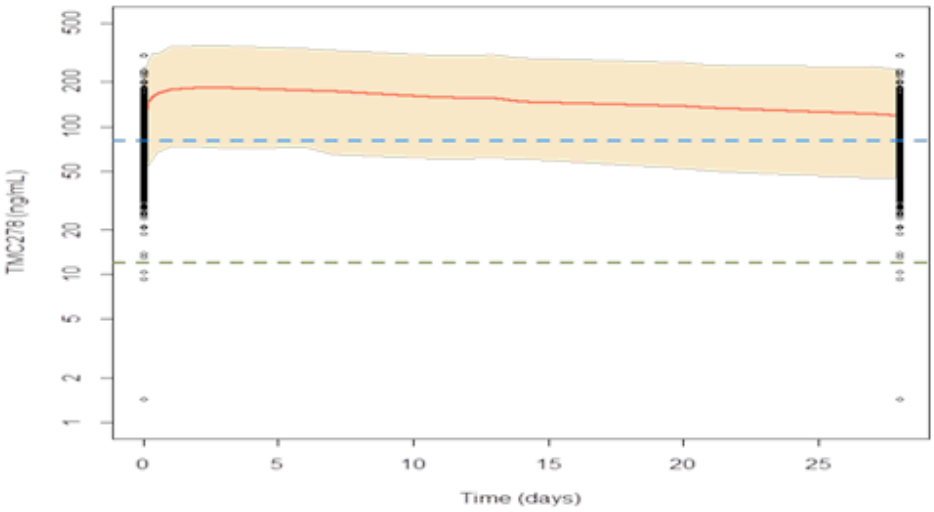
TMC278 LA

During the Maintenance Period, subjects will receive either IM injections of TMC278 LA 600 mg every 4 weeks (Q4W) or TMC278 LA 900 mg every 8 weeks (Q8W). The selection of the TMC278 LA dosing regimens is based on achieving RPV plasma concentrations in the range of those observed with oral RPV 25 mg once daily in HIV-infected patients (mean (SD) C_{trough} of 80 (36) ng/mL in pooled Phase III studies (RPV + 2 NRTIs); and 77 (34) ng/mL in the Maintenance Phase of LAI116482 (RPV + GSK744), as well as constructing a regimen that is most practical for patients, i.e. by reducing the number of dosing/clinic visits while maintaining an acceptable injection volume.

Figure 3 and Figure 4 show the model-predicted RPV plasma concentrations over a dosing interval at steady-state with the respective Q4W and Q8W TMC278 LA dosing regimens. The graphs show the mean profile (red curve) with the 90% prediction interval (shaded area). Also indicated are the mean C_{trough} for oral RPV 25 mg once daily in HIV-infected patients (Phase III, 80 ng/mL) and the protein-binding adjusted IC_{90} for RPV (12 ng/mL), as well as a scatter of the individual C_{trough} values (plotted both at the beginning and at the end of the TMC278 LA dosing interval) in HIV-infected patients (Phase III).

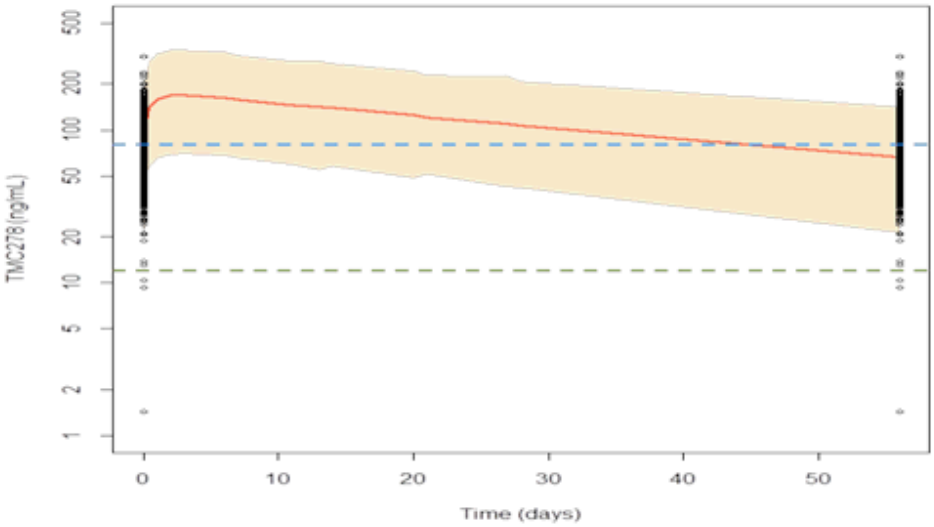
For the simulations, a pharmacokinetic model was used based on all available data from studies with the current TMC278 LA formulation (TMC278-C158, SSAT040, LAI115428) and the population PK model of RPV. With this model, the TMC278 LA dosing regimen (i.e., 4 weeks RPV 25 mg every day followed by IM injections every 4 weeks of TMC278 LA 600 mg) was simulated for 100 subjects. For each of these individuals, the median Ct between day 168 (i.e. after injection 5) and day 336 (i.e., after injection 11) was determined, and from these median values, the mean across subjects was calculated [GlaxoSmithKline Document Number 2011N112455_03: LAI115428].

Figure 3 Model-Predicted Mean (90% prediction interval) TMC278 Plasma Concentration-Time Profile at steady-state after Q4W IM injections of TMC278 LA 600 mg (immediately following 4 weeks oral RPV 25 mg once daily)



Red line represents the predicted mean steady state C_{trough} concentration.
Blue dotted line represents mean C_{trough} for oral RPV 25 mg once daily ;
Green dotted line represents protein-binding adjusted IC90 for RPV;
Black open circles represent individual C_{trough} values with oral RPV 25 mg once daily

Figure 4 Model-Predicted Mean (90% prediction interval) TMC278 Plasma Concentration-Time Profile at steady-state after Q8W IM injections of TMC278 LA 900 mg (immediately following 4 weeks oral RPV 25 mg once daily)



Red line represents the predicted mean steady state C_{trough} concentration.
Blue dotted line represents mean C_{trough} for oral RPV 25 mg once daily;
Green dotted line represents protein-binding adjusted IC90 for RPV;
Black open circles represent individual C_{trough} values with oral RPV 25 mg once daily

TMC278 LA Q8W

For the Q8W TMC278 LA dosing regimen, the mean steady-state C_{trough} is predicted to be around 65 ng/mL, as of the 1st injection. Though this is below the mean RPV C_{trough} with oral RPV 25 mg once daily, the range of model-predicted C_{trough} is similar to the range of C_{trough} with oral RPV 25 mg once daily in the RPV Phase III studies (Figure 4) and in LAI116482 (Maintenance). The RPV plasma concentrations are also higher during the larger part of the TMC278 LA dosing interval. Furthermore, all patients are virologically suppressed before switching to the TMC278 LA regimen. In LAI116482, there were 59/160 HIV-infected patients with a RPV C_{trough} (based on population PK modeling) below 65 ng/mL These 59 patients all maintained virologic suppression.

TMC278 LA Q4W

As such, the mean steady-state C_{trough} with theQ4W TMC278 LA dosing regimen is predicted to be around 115 ng/mL. This is above the mean RPV C_{trough} (80 ng/mL) and the mean Cavg (100 ng/mL) for RPV 25 mg once daily (Phase III). Furthermore, the mean RPV plasma concentrations are already above the mean C_{trough} for RPV as of the 1st injection with TMC278 LA 600 mg.

Section 1.10.1.3 TMC278 Benefit Risk

Revised to (changes struck through and underlined).

Rash

Some observations of ~~grade 1 and 2 rashes~~ rash with RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2).

Section 1.10.1.6 Efficacy Risk

Original text:

This study employs an induction / maintenance approach to the treatment of HIV-1 infection. Following virologic suppression, subjects will be transitioned off of a 3 drug ART regimen to a 2 drug ART regimen. Although both GSK744 and TMC278 have demonstrated antiviral activity in large clinical studies and the two drug combination is currently being evaluated in study 200056, the risk of virologic failure is unknown. Viral loads will be closely monitored throughout the study.

Doses of the GSK744 LA and TMC278 LA have been selected to achieve exposures similar to the oral formulations. Pharmacokinetics will be closely monitored throughout the study.

Revised text:

This study employs an induction / maintenance approach to the treatment of HIV-1 infection. Following virologic suppression, subjects will be transitioned off of a 3 drug ART regimen to a 2 drug ART regimen. Although both GSK744 and TMC278 have demonstrated antiviral activity in large clinical studies and the two drug combination has demonstrated antiviral activity in study LAI116482, the risk of virologic failure in study 200056 is unknown. Viral loads will be closely monitored throughout the study.

Doses of the GSK744 LA and TMC278 LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral formulations. Neither GSK744 LA or TMC278 LA, at any dose, has been used in HIV-1 infected subjects. Plasma samples will be collected throughout the Maintenance Period for determination of GSK744 and TMC278 concentration and possible pharmacokinetic correlation with virologic response.

Section 1.10.2 Benefit Assessment

Revised to (changes struck through and underlined).

Efficacy of the two-drug regimen, as oral agents, ~~will be~~has been demonstrated through Week 48 of the ongoing LAI116482 study ~~prior to the initiation of this study~~.

Section 2 - Objectives and Endpoints

Original text:

Objective	Endpoint
Primary	
To evaluate the efficacy, tolerability, and safety of a regimen of GSK744 LA 400 mg IM plus TMC278 LA 600 mg IM every 4 weeks, relative to GSK744 30 mg plus ABC/3TC orally once daily, through Week 24 of the Maintenance Period.	The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 24 based on intent to treat-exposed (ITT-E) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm.
	Incidence and severity of AEs and laboratory abnormalities over time.
Secondary	
To evaluate the antiviral activity, tolerability, and safety of GSK744 30 mg plus ABC/3TC orally once daily through the Induction and Maintenance Periods.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.

Objective	Endpoint
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).
	Incidence and severity of AEs and laboratory abnormalities over time.
	Absolute values and changes in laboratory parameters over time.
To evaluate the impact of the duration of virologic suppression with GSK744 30 mg plus ABC/3TC orally once daily during the 16 and 24 week Induction Period, on the ability of a regimen of GSK744 LA 400 mg IM plus TMC278 LA 600 mg IM every 4 weeks to maintain virologic suppression through Week 96 of the Maintenance Period.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).
To evaluate the efficacy, tolerability, and safety of a regimen of GSK744 LA 400 mg IM plus TMC278 LA 600 mg IM every 4 weeks, relative to GSK744 30 mg plus ABC/3TC orally once daily, through Week 96 of the Maintenance Period.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death.
	Incidence and severity of AEs and laboratory abnormalities over time.
	Absolute values and changes in laboratory parameters over time.
To evaluate achievement of steady state for GSK744 LA and TMC278 LA regimens.	Determination of achievement of steady state following GSK744 LA and TMC278 LA administration.
To characterize the PK profile (Ctrough) of	Plasma GSK744 and rilpivirine trough

Objective	Endpoint
GSK1265744 and rilpivirine and to explore exposure-response relationships (e.g., the relationship between GSK744 and TMC278 plasma exposure and virologic response or occurrence of adverse events [AEs] through Week 48 of the Maintenance Period.	concentrations over time during the Maintenance Period.
To assess the development of viral resistance in subjects experiencing protocol defined virologic failure.	Incidence of treatment emergent genotypic and phenotypic resistance to GSK744, TMC278, and other on-study ART.
To explore the effect of various demographic Baseline characteristics and adherence on virologic response of GSK744 and TMC278 over time.	Proportion of subjects with plasma HIV-1 RNA <50 c/mL over time.
To evaluate the treatment satisfaction for subjects on the long-acting injectable regimen with those on the oral regimen through Week 96 of the Maintenance Period.	Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time.
To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 24 of the Maintenance Period.	Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time.
To evaluate medication adherence over time.	Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.

Revised text:

Objective	Endpoint
Primary	
To select an intramuscular dosing regimen of GSK744 LA plus TMC278 LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to GSK744 30 mg plus ABC/3TC orally once daily.	The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 based on intent to treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm. Proportion of subjects with protocol defined virologic failures over time

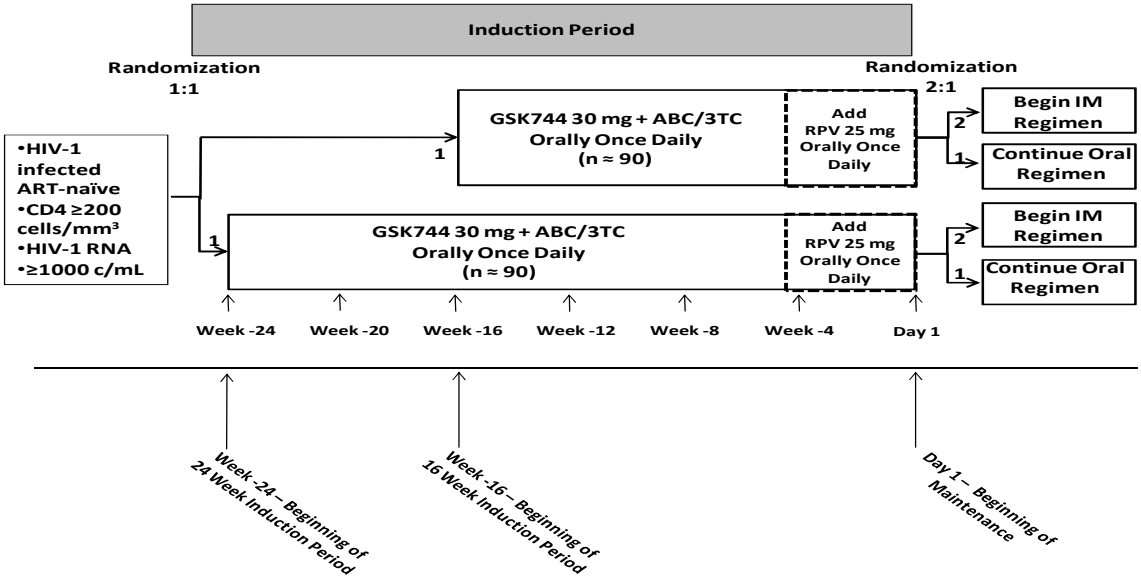
Objective	Endpoint
	Incidence and severity of AEs and laboratory abnormalities over time.
Secondary	
To evaluate the antiviral activity, tolerability, and safety of GSK744 30 mg plus ABC/3TC orally once daily through the Induction and Maintenance Periods.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Absolute values and change from Baseline in plasma HIV-1 RNA. Absolute values and changes from Baseline in CD4+ cell counts. Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.
To evaluate the efficacy, tolerability, and safety of GSK744 LA 400 mg IM plus TMC278 LA 600 mg IM every 4 weeks and GSK744 LA 600 mg IM plus TMC278 LA 900 mg every 8 weeks, relative to GSK744 30 mg plus ABC/3TC orally once daily, through Week 96 of the Maintenance Period.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Proportion of subjects with protocol defined virologic failures over time
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death.
	Incidence and severity of AEs and laboratory abnormalities over time.
	Absolute values and changes in laboratory parameters over time.
To characterize GSK744 LA and TMC278 LA	Plasma PK parameters for GSK744 LA and

Objective	Endpoint
PK and to explore PK-PD relationships.	TMC278 LA (C_{trough} and concentrations post dose [~Cmax]) during the Maintenance Period. Plasma GSK744 and RPV trough concentrations will be used to determine when steady state is achieved for each GSK744 LA and TMC278 LA regimen. Relationship between plasma PK parameters and plasma HIV-1 RNA, CD4+ cell counts and/or occurrence of adverse events [AEs] through Week 48 of the Maintenance Period will be explored.
To assess the development of viral resistance in subjects experiencing protocol defined virologic failure.	Incidence of treatment emergent genotypic and phenotypic resistance to GSK1265744, TMC278, and other on-study ART.
To explore the effect of various demographic Baseline characteristics and adherence on virologic response of GSK1265744 and TMC278 over time.	Proportion of subjects with plasma HIV-1 RNA <50 c/mL over time.
To evaluate the treatment satisfaction for subjects on the long-acting injectable regimens with those on the oral regimen through Week 96 of the Maintenance Period.	Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time.
To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 32 of the Maintenance Period.	Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time.
To evaluate medication adherence over time.	Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.

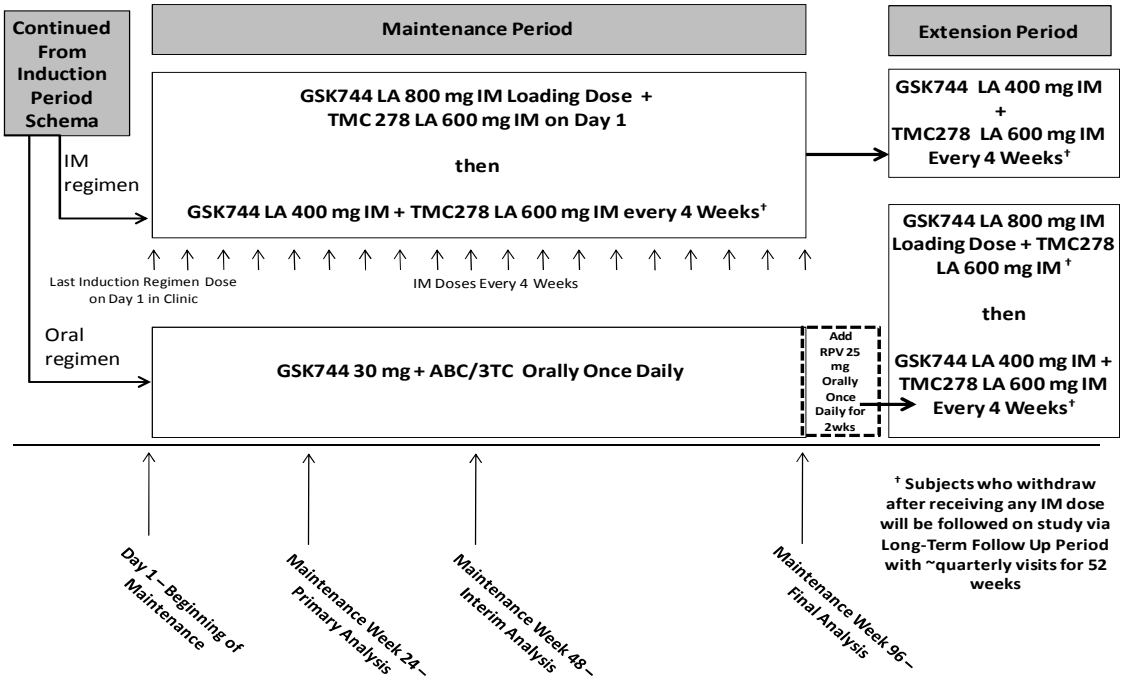
Section 3.1 - Study Design Schematic

Original text:

Induction Period

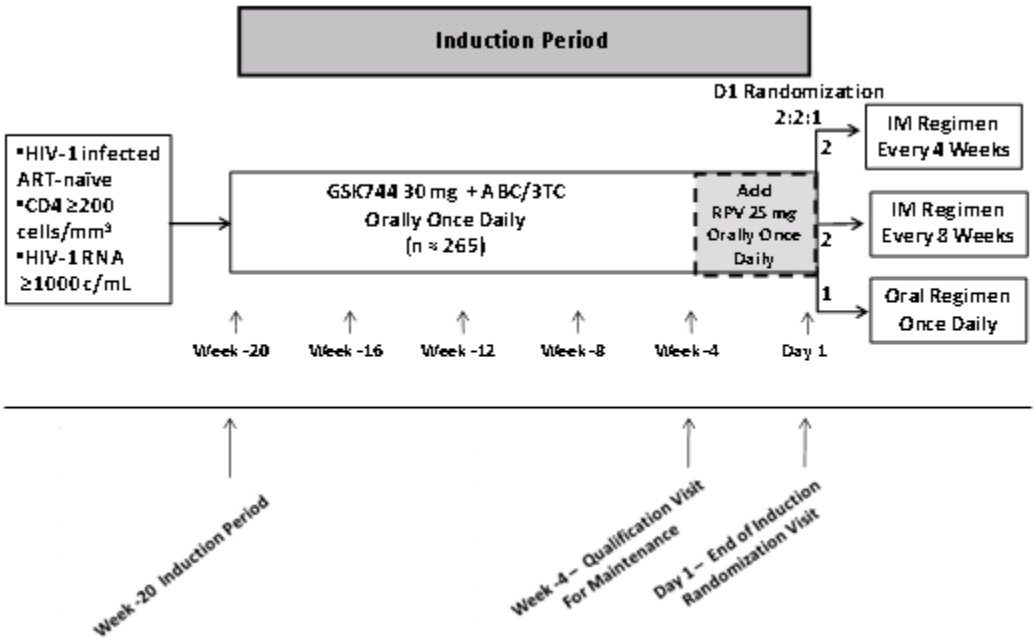


Maintenance and Extension Period

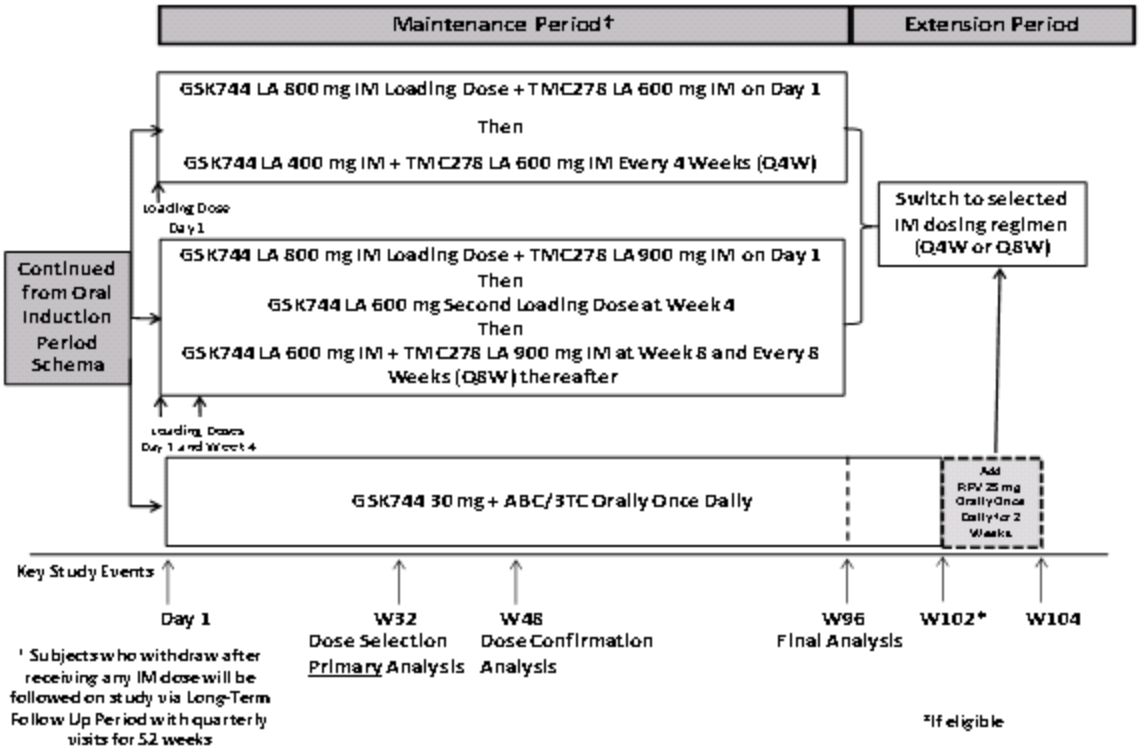


Revised text:

Induction Period



Maintenance and Extension Period



Section 3.2 - Study Design

Revised to (changes struck through and underlined).

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Study 200056 is a Phase IIb, randomized, multicentre, parallel group, open-label, three-part study ~~to be conducted~~ in ~~approximately 180~~ HIV-1 infected ART-naive adults. The study will enroll approximately 265 subjects in order to randomize approximately 225 subjects at Day 1.

This study will consist of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn subjects only).

A subject is considered to have completed the study if they complete the Induction and Maintenance Period through Week 96.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Section 3.2.2 - Induction Period

Original text:

Following the Screening Period, eligible subjects will be randomized 1:1 to either 16 or 24 weeks of induction of virologic suppression utilizing an oral regimen of GSK744 30 mg once daily plus ABC/3TC 600/300 mg once daily. Randomization will be stratified by screening HIV-1 RNA (<100,000 c/mL or ≥100,000 c/mL).

Subjects first day on study treatment will be either Weeks (-24) or Weeks (-16) depending on the outcome of randomization. Further weeks of treatment throughout the Induction Period will be counted up to Day 1 (Day 1 initiates the Maintenance Period).

Example: First day on study Week (-16)

Next visit Week (-12)

Next visit Week (-8), etc

Subjects will initiate treatment on their first day on study and will be seen every 4 weeks for study treatment dispensing and safety and efficacy assessments (see Time and Events Section 6.1 or Section 6.2).

Revised text:

Following the Screening Period, eligible subjects will be enrolled into the study and begin a 20 week Induction Period utilizing an oral regimen of GSK744 30 mg once daily plus ABC/3TC 600/300 mg once daily.

Week -20 is considered the Baseline visit and is the first day on study treatment. Further weeks of treatment throughout the Induction Period will be counted up to Day 1 (Day 1 initiates the Maintenance Period).

Example: First day on study Week (-20)

Next visit Week (-16)

Next visit Week (-12), etc

Subjects will initiate treatment at Baseline (Week -20) and will be seen every 4 weeks for study treatment dispensing and safety and efficacy assessments (see Time and Events Section 6.1).

Section 3.2.3 - Eligibility for the Maintenance Period

Revised to (changes struck through and underlined).

<u>All s</u>ubjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Period.

And:

The medical monitor may advise the site to withdraw a subject from the study prior to Week (-4) to avoid initiating RPV in a subject who is unlikely to be eligible for the Maintenance Period.

In addition to the viral load criteria above, if in the opinion of the Investigator, a subject experiences a significant safety event while taking either GSK744 or RPV, Maintenance eligibility will be determined ONLY in consultation with the medical monitor. **Any rash that is possibly related to study drug, and is present between Week (-4) and Day 1, must be discussed with the Medical Monitor prior to initiation of GSK744 LA or TMC278 LA (See Section 6.10.6.15).**

Subjects ineligible for the Maintenance Period will be withdrawn.

And:

Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Maintenance Period ~~due to incomplete virologic suppression.~~

Section 3.2.4 - Maintenance Period

Original text:

At Day 1, the Maintenance Period begins. Eligible subjects will be randomized a second time 2:1 to receive either an IM regimen of GSK744 LA 400 mg + TMC278 LA 600 mg every 4 weeks or to continue on the oral Induction Period regimen of GSK744 30 mg + ABC/3TC for 96 weeks. This second randomization will be stratified by subjects' previous randomized length of induction and by their screening HIV-1 RNA (<100,000 c/mL or ≥100,000 c/mL).

On the first day of the Maintenance Period (Day 1), subjects will receive their last dose of GSK744+ABC/3TC+RPV in the clinic and initiate either IM injections or be dispensed the oral regimen depending on the randomization arm. Add-on RPV treatment will be discontinued for all subjects after Day 1.

Those subjects randomized to begin treatment with GSK744 LA + TMC278 LA will first receive a loading dose of GSK744 LA 800 mg (delivered as two 400 mg IM injections) as well as TMC278 LA 600 mg IM. Thereafter, subjects will receive GSK744 LA 400 mg IM + TMC278 LA 600 mg IM every 4 weeks for 96 weeks.

Those subjects randomized to continue treatment with GSK744 + ABC/3TC will be dispensed this regimen as per the Time and Events Schedule Section 6.2.

All subjects are then seen approximately every 4 weeks for dosing / dispensing and safety, efficacy and PK assessments for 24 weeks.

Thereafter, subjects on the GSK744 LA + TMC278 LA arm will continue to be seen every 4 weeks for dosing, safety, efficacy and PK assessments through Week 96. Subjects on the GSK744+ABC/3TC arm will be seen in the clinic at Weeks 32, 40, 48,

60, 72, 84 and 96 for dosing, safety, efficacy and / or PK assessments. These subjects will also be assessed for safety via phone interview at Weeks 28, 36, 44, 52, 56, 64, 68, 76, 80, 88 and 92.

See the Time and Events Schedule Section 6.2 and Section 6.3 for more information.

Revised text:

At Day 1, the Maintenance Period begins. Eligible subjects will be randomized 2:2:1 to receive an IM regimen of GSK744 LA 400 mg + TMC278 LA 600 mg every 4 weeks for 96 weeks, an IM regimen of GSK744 LA 600 mg + TMC278 LA 900 mg every 8 weeks for 96 weeks, or to continue on the oral Induction Period regimen of GSK744 30 mg + ABC/3TC once daily for 96 weeks (or 104 weeks if continuing on to the Extension Period). Subject randomization will be stratified by subjects' HIV-1 RNA prior to Week (-8) (<50 c/mL, yes or no).

On the first day of the Maintenance Period (Day 1), subjects will receive their last dose of the Induction regimen (GSK744+ABC/3TC+RPV) in the clinic and initiate either IM injections or be dispensed the oral regimen depending on the randomization arm. Add-on RPV treatment will be discontinued for all subjects after Day 1.

Dosing for each arm is as follows (all injections are single injections unless otherwise noted):

- IM injections every 8 weeks (Q8W)
    - Day 1 only – GSK744 LA 800 mg (loading dose delivered as two 400 mg IM injections) + TMC278 LA 900 mg IM
    - Week 4 only - GSK744 LA 600 mg IM (second loading dose, no TMC278)
    - Week 8 - GSK744 LA 600 mg IM + TMC278 LA 900 mg IM every 8 weeks for 96 weeks
- IM injections every 4 weeks (Q4W)
    - Day 1 only - GSK744 LA 800 mg (loading dose delivered as two 400 mg IM injections) + TMC278 LA 600 mg IM
    - Week 4 - GSK744 LA 400 mg IM + TMC278 LA 600 mg IM every 4 weeks for 96 weeks
- Oral Control Arm
    - GSK744 30 mg + ABC/3TC once daily for 96 weeks (or 104 weeks if continuing on to the Extension Period)

It is important to note that keeping to the subject's visit schedule is a very important component to the study. IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). A (+ or -) 7 day window is allowable for IM dosing but not preferred. Oral dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Baseline visit).

All subjects are seen approximately every 4 weeks for safety, efficacy and PK assessments through Week 32. After Week 32, subjects will continue to be seen as per the Time and Events Schedule (see Section 6) for dosing, safety, efficacy and PK assessments through Week 96 (or Week 104 for the oral arm if subject is continuing on to the Extension Period).

Some visits that are not aligned with dosing will be conducted by telephone interview. This allows for safety assessments to be conducted at all visits, but limits clinic visits for non-dosing visits. Telephone safety assessments will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including injection site reactions or oral compliance issues. Telephone visits will be clearly noted in the Time and Events Schedule.

See the Time and Events Schedule Section 6.2 and Section 6.3 for more information. See Section 3.2.5.2 for additional information regarding special requirements from Week 96 to Week 104 for subjects on the oral arm entering the Extension Period

If one of the IM dosing regimens (Q4W or Q8W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued dosing regimen may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

Section 3.2.5 - Extension Period

Original text:

Entering From the GSK744 LA + TMC278 LA Arm

All subjects who successfully complete 96 weeks of GSK744 LA + TMC278 LA treatment in the Maintenance Period will continue to have access to both GSK744 LA 400 mg IM and TMC278 LA 600 mg IM every 4 weeks via the Extension Period until it is either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated. At Week 96, these subjects will continue to receive GSK744 LA 400 mg IM and TMC278 LA 600 mg IM every 4 weeks for the remainder of study participation. Safety and efficacy assessments will be conducted every 4 weeks until Week 112. These assessments will then be quarterly for the remainder of the study (dosing and AE assessments remain every 4 weeks). See the Time and Events Schedule Section 6.5 for more information.

Entering From the GSK744 + ABC/3TC Arm

All subjects who successfully complete 96 weeks of GSK744 + ABC/3TC treatment in the Maintenance Period will have the option to either continue study participation by switching to GSK744 LA + TMC278 LA in the Extension Period, or to discontinue from the study.

Subjects not choosing to switch to the long acting regimen will complete their study participation.

Subjects who choose to continue on to the Extension Period will need to be assessed for eligibility to begin the GSK744 LA + TMC278 LA regimen. Subjects must have an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit in order to be eligible to enter the Extension Period. Subjects with an HIV-1 RNA ≥ 50 c/mL may be allowed to enter the Extension Period at the discretion of the medical monitor or may be withdrawn.

Subjects eligible to enter the Extension Period will add a short course (2 weeks) of RPV 25 mg orally once daily to their GSK744 + ABC/3TC regimen at Week 98 before initiating dosing with the long acting regimen at Week 100. This allows these subjects to achieve steady state of RPV prior to beginning the long acting regimen. Therefore, for the first 2 weeks of the Extension Period, subjects will remain on their oral Maintenance Period regimen until eligibility is confirmed. If eligible, subjects will be taking GSK744 + ABC/3TC + RPV from Week 98 to Week 100 of the Extension Period.

At Week 100, subjects will receive their last dose of GSK744 + ABC/3TC + RPV in the clinic and will receive a loading dose of GSK744 LA 800 mg (delivered as two 400 mg IM injections) as well as TMC278 LA 600 mg IM. At Week 104, subjects will receive GSK744 LA 400 mg IM + TMC278 LA 600 mg IM every 4 weeks until it is either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated. Safety and efficacy assessments will be conducted every 4 weeks until Week 112. These assessments will then be quarterly for the remainder of the study (dosing and AE assessments remain every 4 weeks). See the Time and Events Schedule Section 6.3 and Section 6.5 for more information.

Revised text:

A single IM dosing regimen will be selected as according to the RAP to be evaluated in the Extension period.

Entering From the GSK744 LA + TMC278 LA Arm

All subjects who successfully complete 96 weeks of GSK744 LA + TMC278 LA treatment in the Maintenance Period will continue to have access to both GSK744 LA and TMC278 LA in the Extension Period until study treatment is eitherlocally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated.

Subjects will be switched to the selected dose at Week 96 and will continue to receive the selected IM dosing regimen for the remainder of study participation. Safety and efficacy assessments will be conducted every 16 weeks after the initial switch. Dosing visits will occur according to the selected dosing regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.

Entering From the GSK744 + ABC/3TC Arm

All subjects who successfully complete 96 weeks of GSK744 + ABC/3TC treatment in the Maintenance Period will have the option to either continue study participation by switching to GSK744 LA + TMC278 LA in the Extension Period, or to complete their study participation at Week 96 (no withdraw visit needed).

Subjects who choose to continue on to the Extension Period will need to be assessed for eligibility to begin the selected GSK744 LA + TMC278 LA regimen. Subjects will continue on their Maintenance regimen (GSK744 + ABC/3TC) while eligibility is being confirmed. The Week 100 HIV-1 RNA result will be used to determine eligibility and subjects will have a visit at approximately (depending on availability of results) Week 102 to assess eligibility. All subjects with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 100 visit are eligible to enter the Extension Period. Note: Subjects with an HIV-1 RNA ≥ 50 c/mL result from the Week 100 visit may be allowed to enter the Extension Period only at the discretion of the medical monitor or withdrawn.

Subjects eligible to enter the Extension Period will add a short course (2 weeks) of RPV 25 mg orally once daily to their GSK744 + ABC/3TC regimen at Week 102 before initiating dosing with the long acting regimen at Week 104. This allows subjects to achieve steady state of RPV prior to beginning the long acting regimen.

At Week 104, subjects will receive their last dose of GSK744 + ABC/3TC + RPV in the clinic and will begin IM dosing with the selected the IM regimen. These subjects will receive loading doses as per the requirement of the selected regimen (see Section 5.1.6 for dosing regimens).

Subjects will continue study treatment until GSK744 LA and TMC278 LA are either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated. Safety and efficacy assessments will be conducted every 16 weeks after the initial switch . Dosing will occur according to the selected regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.

Subjects not eligible to enter the Extension Period will end their study participation (Week 102 will be the last study visit, no withdraw visit needed). Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

Section 3.2.8 - Independent Data Monitoring Committee

Revised to (changes struck through and underlined).

In addition, futility guidance (e.g., a Bayesian posterior probability approach when 50% of subjects have completed Week 24 of the Maintenance Period) is included to monitor the performance of all treatment arms in order to prevent subjects from continuing on a dosing regimen if existing data indicates that subjects are at unacceptable risk of inadequate maintenance of virologic suppression. ~~Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.~~If one of the IM dosing regimens (Q4W or Q8W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued dosing regimen may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

As subjects enter the Maintenance Period of the study, if the number of failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

Section 3.2.9 - Primary Analysis

Revised to (changes struck through and underlined).

The primary analysis will be conducted when all subjects have completed their Maintenance Period Week 32~~24~~ visit. This analysis will characterize the safety, tolerability and durability of antiviral response ~~combining data~~ from both the Induction Period and the Maintenance Period. Planned analyses will also be conducted at Week 48 and Week 96. Follow-up analyses of data collected after subjects have entered into the Extension Period may be conducted to more fully characterize the long-term safety and efficacy profile of GSK1265744 and TMC278. ~~Additional analyses, for example at Day 1, may be conducted to support internal decision making, scientific presentations or regulatory document preparation, as needed.~~

~~Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.~~

Section 3.3 – Discussion of Design

Original text:

Study 200056 is a Phase IIb assessment of a regimen consisting of the long-acting injectable forms of GSK744 and TMC278 to maintain virologic suppression in previously untreated HIV-infected subjects without evidence of transmitted resistance who achieve virologic suppression on GSK744 plus ABC/3TC. The ongoing study LAI116482 provides support for this unique approach of a two-class, two-drug regimen. Results from planned analyses of LAI116482 support the choice of 30 mg GSK744 for use in the Induction Period of this study. Exposure and efficacy data from LAI116482 as well as exposure data from the repeat dose studies with GSK744 LA and TMC278 LA defined the target doses and exposures for GSK744 LA and TMC278 LA during the Maintenance Period. Systemic exposure of TMC278 obtained with TMC278 LA is aimed to be comparable to that obtained with RPV, for which the antiviral activity and safety has been well established through Phase III studies.

Long acting GSK744 has been investigated in approximately 134 healthy subjects to date as both SC and IM injections. Long-acting TMC278 has been investigated in approximately 159 healthy subjects to date as both SC and IM injections. This study will be the first evaluation of GSK744 LA or TMC278 LA in HIV-infected subjects. The results to date support GSK744 LA and TMC278 LA for continued clinical development. Injection site reactions (ISR) of both agents have been generally mild, self-limited, and well-tolerated in single and multiple dose studies.

The early results of LAI116482 support the use of oral GSK744 plus NRTIs as a reference regimen to the investigational two-drug long-acting regimen. At Week 24, the response rates (HIV-1 RNA <50 c/mL; ITT, MSDF) for the three doses of GSK744 in the LAI116482 study were 88%, 85% and 87% for the 10 mg, 30 mg, and 60 mg arms, respectively. These rates compare favourably to the control regimen of EFV plus NRTIs in this study where 74% of subjects achieved HIV-1 RNA <50 c/mL at Week 24. The response rates seen at Week 24 are also consistent with a similarly sized study of dolutegravir vs. EFV (ING112276), where each was administered to ART-naive subjects in combination with NRTIs. In the study ING112276, the Week 24 response rates (HIV-1 RNA <50 c/mL) for dolutegravir and efavirenz were 94% and 82%, respectively [GlaxoSmithKline Document Number 2011N117114_01].

The background NRTIs (ABC/3TC) are accepted agents for initiation of antiretroviral therapy in treatment guidelines [EACS, 2012; DHHS, 2013] and as such are considered appropriate for this trial. RPV is approved as Edurant for use in combination ART at an oral dose of 25 mg, once daily with a meal in treatment naive patients [Edurant Product Information, 2012].

This trial is designed to allow for both an evaluation of the antiviral efficacy of two discrete induction periods of GSK744 in combination with a background of NRTIs as well as the evaluation of a long-acting two-drug regimen for the maintenance of previously achieved virologic suppression for 96 weeks while using control regimen of oral GSK744 plus NRTIs. The primary endpoint, proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 24, is a well established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2002]. The Week 48 time point will permit an evaluation of the ability of this investigational two-drug long-acting combination to maintain virologic suppression. Longer term durability of virologic

suppression of this long-acting two-drug regimen will also be evaluated through a formal Week 96 analysis.

Revised text:

Long acting GSK744 has been investigated in 136 healthy subjects to date as both SC and IM injections. This study will be the first evaluation of GSK744 LA or TMC278 LA in HIV-infected subjects. The results to date support GSK744 LA and TMC278 LA for continued clinical development. Injection site reactions (ISR) of both agents have been generally mild, self-limited, and well-tolerated in single and multiple dose studies.

The results of LAI116482 support the use of oral GSK744 plus NRTIs as a reference regimen to the investigational two-drug long-acting regimen. At the primary endpoint of Week 48, the response rates (HIV-1 RNA <50 c/mL; ITT, MSDF, Table 1) for the three doses of GSK744 in the LAI116482 study were 80%, 80% and 87% for the 10 mg, 30 mg, and 60 mg arms, respectively. These rates compare favorably to the control regimen of EFV plus NRTIs in this study where 71% of subjects achieved HIV-1 RNA <50 c/mL at Week 48.

These data indicate continued viral suppression after 24 weeks of the two drug GSK744 and RPV regimen.

The ITT-Maintenance Exposed (ITT-ME) Population consists of all randomized subjects who received at least one dose of investigational product during the Maintenance Phase of the study. Of the subjects who entered the Maintenance Phase of the study, the majority remained suppressed through Week 48 (24 weeks of two drug therapy) (Table 3).

Table 3 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-ME Population)

Visit	GSK744 10 mg N=52 n (%)	GSK744 30 mg N=53 n (%)	GSK744 60 mg N=55 n (%)	GSK744 Subtotal N=160 n (%)	EFV 600 mg N=47 n (%)
Week 16 - Induction	50 (96)	49 (92)	52 (95)	151 (94)	43 (91)
Week 24 - Induction	50 (96)	50 (94)	53 (96)	153 (96)	45 (96)
Week 48 - Maintenance	48 (92)	48 (91)	53 (96)	149 (93)	44 (94)

The background NRTIs (ABC/3TC) are accepted agents for initiation of antiretroviral therapy in treatment guidelines [EACS, 2012; DHHS, 2013] and as such are considered appropriate for this trial. RPV is approved as Edurant for use in combination ART at an oral dose of 25 mg, once daily with a meal in treatment naive patients [Edurant Product Information, 2013].

This trial is designed to evaluate two distinct periods. First, to evaluate the ability of GSK744 + background NRTIs to induce virologic suppression during the Induction Period. Second, during the Maintenance Period, two different dosing strategies of a long-acting, two-drug, two-class regimen will be evaluated on their ability to maintain

virologic efficacy for 96 weeks compared to a control regimen of oral GSK744 + ABC/3TC.

The primary endpoint, proportion of subjects with plasma HIV-1 RNA < 50 c/mL, is a well established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2002]. The primary endpoint for this study is proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 32 and will be used to select an IM dosing regimen (Q8W or Q4W). Week 32 has been selected to allow a comparable evaluation among the dosing regimens. Q8W begins dosing at Week 8, following a loading dose at Day 1 and Week 4. Therefore choosing Week 32 as an endpoint allows for a 24 week evaluation of the Q8W arm at steady state.

The Week 48 analysis will permit an evaluation of the ability of the investigational two-drug long-acting combinations to maintain virologic suppression over time, and will serve as the dose confirmation of the dosing regimen selected at Week 32. Longer term durability of virologic suppression for these long-acting two-drug regimens will also be evaluated through a formal Week 96 analysis.

Section 4.1 - Number of Subjects

Original text:

Sufficient subjects will be screened (approximately 260) in order to ensure that a total of approximately 180 subjects will be randomized at the beginning of the Induction Period, (approximately 90 to each treatment arm).

Revised text:

Sufficient subjects will be screened (approximately 350) in order to ensure that a total of approximately 265 subjects areenrolled at the beginning of the Induction Period and to ensure approximately 225 subjects are randomized into the Maintenance Period.

Section 4.2 – Inclusion Criteria

Revised to (changes struck through and underlined).

Criteria 2b.

2. A female subject is eligible to enter and participate in the study if she:

    b. is of child-bearing potential with a negative pregnancy test at both Screening and first day of the Induction Period ~~[either Week (-16) or Week (-24)]~~ and agrees to use one of the following methods of contraception to avoid pregnancy 2 weeks prior to administration of IP, throughout the study, and for at least 2 weeks after discontinuation of all oral study medications and for at least 52 weeks after discontinuation of GSK744 LA and TMC278 LA

Section 4.3 – Exclusion Criteria

Revised to (changes struck through and underlined).

Subjects with known moderate to severe hepatic impairment. ~~Subjects with known hepatic impairment must be assessed using the Child-Pugh classification and must be excluded if found to be Class B or C classification [Pugh, 1973].~~

Added:

Notwithstanding these minimum inclusion and exclusion criteria, investigators must also follow country specific guidelines where they exist when making decisions about subjects who are eligible for study participation.

Section 4.5 - Withdrawal Criteria

Revised to (changes underlined).

Added:

Subjects permanently discontinuing study treatments prior to Week 96 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects permanently discontinuing participation from the Extension and Long-Term Follow-Up Period prior to commercially available drug supply are considered to be withdrawn from the study treatments and also from the study.

And:

Subjects must be withdrawn from the study for any of the following reasons:

- Subjects who do not wish to continue on the remaining dosing regimen if one dosing regimen is discontinued further to an IDMC decision (see Section 3.2.8).
- Liver toxicity where Stopping Criteria as described in Section 6.10.3 are met and no compelling alternative cause is identified.
- Renal toxicity as specified in Section 6.10.6.9 and Section 6.10.6.10 is met and no compelling alternate cause is identified.

Section 5.1.1 - GSK1265744 – Tablet (GSK744)

Revised to (changes underlined).

GSK744 is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an induction seal.

Section 5.1.4 - GSK1265744 – Injectable Suspension (GSK744 LA)

Revised to (changes struck through and underlined).

GSK744 LA is manufactured by GlaxoSmithKline and is a sterile white to slightly colored suspension containing 200 mg/mL of GSK744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and aluminium seal. Each vial is for single use containing a ~~nominal~~ withdrawable ~~fill~~ volume of ~~1.5 mL or~~ 2.0 mL, and does not require dilution prior to administration. GSK744 LA injectable suspension is to be stored at up to 30°C, do not freeze.

Section 5.1.6 - Dosage and Administration

Original text:

Following is a table of dosing and administration for all treatment arms:

Background NRTI combination and Investigational Product	**Dose and Dose Interval**
Induction Period – RPV to be taken with a meal	
16 week Induction Arm	
ABC/3TC	1 X 600 mg / 300 mg tablet once daily from Week (-16) through Day 1 of Maintenance (Day 1 taken in clinic)
GSK744	1 X 30 mg tablet once daily from Week (-16) through Day 1 of Maintenance (Day 1 taken in clinic)
RPV	1 X 25 mg tablet once daily from Week (-4) through Day 1 of Maintenance (Day 1 taken in clinic)
24 week Induction Arm	
ABC/3TC	1 X 600 mg / 300 mg tablet once daily from Week (-24) through Day 1 of Maintenance (Day 1 taken in clinic)
GSK744	1 X 30 mg tablet once daily from Week (-24) through Day 1 of Maintenance (Day 1 taken in clinic)
RPV	1 X 25 mg tablet once daily from Week (-4) through Day 1 of Maintenance (Day 1 taken in clinic)
Maintenance Period – no food requirements	
GSK744 LA + TMC278 LA Dosing Arm	
GSK744 LA	2 X 2 mL Injections (4 mL [800 mg] total) intramuscularly (IM) as loading dose (Day 1 only) followed by 1 X 2 mL injection (400 mg) IM every 4 weeks for 96 weeks
TMC278 LA	1 X 2 mL Injection (600 mg) intramuscularly every 4 weeks for 96 weeks
Oral Control Arm	
ABC/3TC	1 X 600 mg / 300 mg tablet once daily for 96 weeks
GSK744	1 X 30 mg tablet once daily for 96 weeks
Extension Period	
GSK744 LA + TMC278 LA Dosing Arm – no food requirements	
GSK744 LA	1 X 2 mL injection (400 mg) IM every 4 weeks*

Background NRTI combination and Investigational Product	**Dose and Dose Interval**
TMC278 LA	1 X 2 mL Injection (600 mg) IM every 4 weeks*
following Oral Control Arm – RPV to be taken with a meal	
RPV	1 X 25 mg tablet once daily from Week 98 through Week 100
GSK744 LA	2 X 2 mL Injection (4 mL [800 mg] total) as loading dose (Week 100 only) followed by 1 X 2mL injection (400 mg) IM every 4 weeks*
TMC278 LA	1 X 2 mL injection (600 mg) IM every 4 weeks (starting at Week 100)*

*until it is either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of GSK744 or TMC278 is terminated

Revised text:

Following is a table of dosing and administration for all treatment arms:

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injections (No TMC278 LA)

Week 8 to Week 88 (2 injections every 8 weeks)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
Week 4 to Week 92 (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
GSK744 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
If continuing to Extension Period:	
Week 96 to Week 102 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
If eligible to enter Extension Period:	
Week 102 to Week 104 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal
Extension Period (Week 96 plus+)	
If GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks is selected:	
Week 96 plus+ (2 injections every 8 weeks)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection

If switching from Oral Arm:	
Week 104 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
Week 108 – 2nd loading dose (1 injection once)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injections (No TMC278 LA)
Week 112 plus+ (2 injections every 8 weeks)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
If GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks is selected:	
Week 96 plus+ (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm:	
Week 104 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
Week 108 plus+ (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection

* Or through Week 104 if eligible to enter the Extension Period.
+ until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of GSK744 or TMC278 is terminated

Section 5.1.7 - Dosing Considerations for GSK744 LA + TMC278 LA

Revised to (changes struck through and underlined).

IM injections should be administered at a 90 degree angle into the gluteus medius muscle using a 1.5" 25 gauge needle for GSK744 LA and a 1.5" 21 gauge needle for TMC278 LA <u>in most subjects</u>. The needle should be long enough to reach the muscle mass and prevent study drug from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. <u>Longer needle lengths will be required for subjects with higher body mass indexes (BMIs, example > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously</u>. <u>BMI and needle length used will be collected in the eCRF.</u>

On Day 1, subject should be dosed with the IM regimen within 2 hours of taking the last Induction regimen dose where possible. The same should apply to subjects switching from the oral regimen to an IM regimen at Week 104.

Should the subject have intolerance to the single 3 mL injection, the injection may be administered as 2 separate 1.5 mL injections with the assent of the medical monitor. If the injection is split, this will be noted in the eCRF and the intolerance captured as an AE.

~~Detailed~~ Additional dosing instructions and considerations can be found in the SPM.

Section 5.2 – Treatment Assignment

Original text:

There are 2 randomizations in the study; both will be stratified by screening HIV-1 RNA (<100,000 or ≥100,000 c/mL). At the first randomization, study eligible subjects will be randomized to their length of induction treatment (either 16 or 24 weeks) at a1:1 ratio. Following completion of their Induction Period, subjects eligible to enter the Maintenance Period will be randomized again to either the GSK744 LA + TMC278 LA arm or the oral control arm (GSK744 + ABC/3TC) at a ratio of 2:1. This second randomization will be stratified by subjects' previous randomized length of induction and by their screening HIV-1 RNA.

Revised text:

Following completion of the Induction Period, subjects eligible to enter the Maintenance Period will be randomized 2:2:1 to Q8W or Q4W of GSK744 LA + TMC278 LA or to the oral control arm (GSK744 + ABC/3TC). Randomization will be stratified by HIV-1 RNA result before Week (-8) (<50 c/mL yes or no).

Section 5.7 - Interruption of Study Treatment and Visit/Dosing Windows

Revised to (changes struck through and underlined).

It is important to note that keeping to the subject's visit schedule is a very important component to the study.

Note: **All decisions regarding dose interruption / resumption must be discussed with the medical monitor in advance.**

~~Should study treatment be interrupted, the following guidance must be used:~~

~~**GSK744 and/or RPV Containing Arms**~~**Oral Dosing**

Oral dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Baseline visit).

And:

~~**GSK744 LA and / or TMC278 LA Containing Arms**~~**IM Dosing**

Plasma concentrations of both drugs may be measurable for approximately 52 weeks following IM injections.

IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred.

~~After a single 800 mg dose of GSK744 LA, concentrations may be measurable for up to 52 weeks and after a single 600 mg dose of TMC278 LA, concentrations may be measurable for up to 24 weeks.~~

~~Dosing frequency during the Maintenance and Extension Periods is scheduled to occur approximately **every 4 weeks (28 days)**. Dose timing with GSK744 LA + TMC278 LA is critical to assure therapeutic drug levels are maintained and therefore the following guidance is provided regarding allowable windows around dosing:~~

- ~~Dosing is expected to occur **within 21-35 days from the previous dose** while simultaneously keeping to the subjects original visit schedule projected from Day 1 of the Maintenance Period (or Week 100 of the Extension Period for oral control arm switch subjects).~~
- ~~Over time, the subject who comes in late in the visit window should return for the next injection on the early side of the window to get back on track with the original projected visit schedule.~~
- Dosing may occur without consultation from the medical monitor if performed within the ~~this dosing~~ ± 7 day window.
- Any request for the visit/dosing to occur outside of the allowed window ~~either ≥36 days or ≤20 days from the previous dose~~ must be discussed and agreed with the medical monitor *prior* to dosing. In the event of a late dose, a revised dosing schedule for subsequent dosing may be required and will be communicated to the site staff at the time of approval for continued dosing. Temporary switch to oral dosing of GSK744 and/or RPV may be an option based on individual subject circumstance as described in Section 5.6.1.
- See the SPM for scheduling guidance and further information and examples.

Section 6 – Time and Events tables

Original text:

Time and Events Table – 24 Week Induction Period

Procedures for the 24 Week Induction	Screening Period [a]	Baseline / Week (-24)	Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
Written Informed Consent	X								a. Complete all Screening assessments within 28 days. Subjects may be randomized and begin the Induction Period as soon as all Screening assessments are complete. Subjects may be rescreened once and will be assigned a new subject number. b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and / or care. c. Measure height at Screening Period only. Measure weight at Screening Period and WD only. d. Measure vital signs after about 5 minutes of rest in a semi-supine position. e. Perform ECG at Baseline in triplicate prior to dosing; preferably 2 – 4 hours post dosing for all other visits. f. Collect full routine medical history plus; cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events, recent [≤6 months] illicit drug use), gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders.
Demography	X								
Eligibility Verification	X	X					X [n]		
Randomization		X							
Physical Exam [b]	X								
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X	X	X and smoking status	
Vital Signs (BP, HR), Weight, Height [c, d]	X	X					X	X	
12-Lead ECG [e]	X pre-dose	X					X	X	
Medical History and CDC Classification [f]	X								
Medication History / Prior ART History	X								

Procedures for the 24 Week Induction	Screening Period [a]	Baseline / Week (-24)	Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
HIV Associated Conditions , AE and SAE Assessment, Concomitant Meds	X [g]	X	X	X	X	X	X	X	g. Collect SAEs at Screen only if associated to study participation. h. Preferably completed at the beginning of the visit. i. Collect for women of childbearing potential only. A negative urine pregnancy test is required prior to beginning the Induction Period. S=Serum/U=Urine j. Plasma for storage will be used: to determine genotypic eligibility at Screen, for possible future analyses, as back- up in case samples are lost or damaged in transit to the lab and for genotypic and phenotypic analyses in cases of virologic failure. k. Overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable. l. Collect PGx sample at Baseline. May be collected later during the study if necessary. m. Instruct subjects to continue to take the Induction regimen (including RPV) through Day 1 of the Maintenance Period. Subjects should be reminded to take the Day 1 dose in the clinic and return the PK diary. The PK diary will be completed for all subjects in case they are randomized to continue on the GSK744 + ABC/3TC arm. n. Confirmation of eligibility to enter the Maintenance Period. See Section 3.2.3. o. Remind subjects of the potential change in study
Columbia Suicide Severity Rating Scale (eC-SSRS) [h]	X	X	X	X	X	X	X	X	
HIVTSQ(s) [h]			X				X	X	
HIVMQ							X		
Chemistry and Hematology	X	X	X	X	X	X	X	X	
Pregnancy Testing[i]	S	U	S	S	S	S	S	S	
HIV-1 RNA and sample for storage [j]	X	X	X	X	X	X	X	X	
CD4+ and CD8+	X	X	X		X		X	X	
Urinalysis and urine microalbumin/creatinine ratio		X					X	X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [k]		X					X	X	
Hepatitis B (HBsAg) and Hepatitis C (anti-HCV Ab), HLA-B*5701	X								
PT/PTT/INR	X	X							

Procedures for the 24 Week Induction	Screening Period [a]	Baseline / Week (-24)	Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
PGx [l]		X							treatment and visit frequency which begins at Day 1.
PK Sample for Storage								X	p. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
Study Treatment Dispensation		X	X	X	X	X	X Add RPV [m]		
Study Treatment Accountability (pill counts)			X	X	X	X	X	X	
RPV and PK Diary Dispensation [m]							X		
Subject Visit Reminder Contact	X	X	X	X	X	X	X [o]	X	
Subject Contact Detail Confirmation	X	X	X	X	X	X	X		

Time and Events Table – 16 Week Induction Period

Procedures for the 16 Week Induction Period	Screening Period [a]	Baseline / Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
Written Informed Consent	X						q. Complete all Screening assessments within 28 days. Subjects may be randomized and begin the Induction Period as soon as all Screening assessments are complete. Subjects may be rescreened once and will be assigned a new subject number. r. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and / or care. s. Measure height at Screening Period only. Measure weight at Screening Period and WD only. t. Measure vital signs after about 5 minutes of rest in a semi-supine position. u. Perform ECG at Baseline in triplicate prior to dosing; preferably 2 – 4 hours post dosing for all other visits. v. Collect full routine medical history plus; cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events, recent [≤6 months] illicit drug use), gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders. w. Collect SAEs at Screen only if associated to study participation. x. Preferably completed at the beginning of the visit.
Demography	X						
Eligibility Verification	X	X			X [n]		
Randomization		X					
Physical Exam [b]	X						
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X and smoking status	
Vital Signs (BP, HR), Weight, Height [c, d]	X	X			X	X	
12-Lead ECG [e]	X pre-dose	X			X	X	
Medical History and CDC HIV-1 Classification [f]	X						
Medication History including Prior ART History	X						
HIV Associated Conditions , AE and SAE Assessment, Concomitant Meds	X [g]	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (eC-SSRS) [h]	X	X	X	X	X	X	
HIVTSQ(s) [h]			X		X	X	

Procedures for the 16 Week Induction Period	Screening Period [a]	Baseline / Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
HIVMQ					X		y. Collect for women of childbearing potential only. A negative urine pregnancy test is required prior to beginning the Induction Period. S=Serum/U=Urine z. Plasma for storage will be used: to determine genotypic eligibility at Screen, for possible future analyses, as back- up in case samples are lost or damaged in transit to the lab and for genotypic and phenotypic analyses in cases of virologic failure. aa. Overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable. bb. Collect PGx sample at Baseline. May be collected later during the study if necessary. cc. Instruct subjects to continue to take the Induction regimen (including RPV) through Day 1 of the Maintenance Period. Subjects should be reminded to take the Day 1 dose in the clinic and return the PK diary. The PK diary will be completed for all subjects in case they are randomized to the oral regimen arm. dd. Confirmation of eligibility to enter the Maintenance Period. See Section 3.2.3. ee. Remind subjects of the potential change in study treatment and visit frequency which begins at Day 1. ff. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [i]	S	U	S	S	S	S	
HIV-1 RNA and sample for storage [j]	X	X	X	X	X	X	
CD4+ and CD8+	X	X	X		X	X	
Urinalysis and urine microalbumin / creatinine ratio		X			X	X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [k]		X			X	X	
Hep B (HBsAg), Hep C (anti-HCV Ab), HLA-B*5701	X						
PT/PTT/INR	X	X					
PGx [l]		X					
PK Sample for Storage						X	
Study Treatment Dispensation		X	X	X	X Add RPV [m]		
Study Treatment Accountability (pill counts)			X	X	X	X	
RPV and PK Diary Dispensation [m]					X		
Subject Visit Reminder Contact	X	X	X	X	X [o]	X	

Procedures for the 16 Week Induction Period	Screening Period [a]	Baseline / Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD [p]	Notes
Subject Contact Detail Confirmation	X	X	X	X	X		

Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA+TMC278 LA)

Procedures For Maintenance – IM regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 29	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [m,n]
Verify Eligibility	X																											
Randomization	X																											
Symptom Directed PE, ISR & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X	X				X			X				X			X			X			X			X	X
Weight	X							X							X												X	X
ECG [c]	X[pre]	X	X	X				X			X				X			X			X			X			X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Diary	D	E	E	E	E	E	E	E	D	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E

Procedures For Maintenance – IM regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 29	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [m,n]
Dispensation and Review [d]																												
Exercise Habit Assessment [e]	X								X																			
eC-SSRS [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIVTSQ(s) [g]	X[pre]		X	X				X							X												X	X
HIVTSQ(c) [g]								X																				X
HIVMQ [g]				X				X							X												X	X [g]
Chemistry and Hematology	X	X	X	X	X	X	X	X	X		X	X	X	X	X			X			X			X			X	X
Pregnancy Testing [h]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	S
HIV-1 RNA & sample for storage [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+/ CD8+	X		X	X				X			X				X			X			X			X			X	X
Urinalysis and urine microalbumin/ creatinine ratio	X							X							X						X						X	X

Procedures For Maintenance – IM regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 29	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [m,n]
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X		X					X							X						X						X	X

Procedures For Maintenance – IM regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 29	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [m,n]
Procedures For Maintenance – IM regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 29	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [m,n]
PT/PTT/INR	X							X							X												X	X
PK Sample [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	S	S	S	S	S	S	S	S	S	S	S	S	S
Study Treatment Administration [o]	X [l]		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam

a) Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.
b) Measure vital signs after about 5 minutes of rest in a semi-supine position.
c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit.
d) D = Daily E = Episodic. Subjects will complete a daily diary of injection site reactions from Day 1 to Week 1 and again from Week 28 to Week 29 (daily). At all other visits subjects will complete a diary only if the subject experiences a reaction (episodic). Subjects will be dispensed a new diary at each visit.
e) Subject's exercise habits will be assessed daily between Day 1 and Week 1 and again between Week 28 and Week 29. Assessments will include type and duration of cardiovascular exercise and duration of any strength or other strenuous exercises. This information will be collected via the daily ISR diary.
f) Preferably completed at the beginning of the visit.
g) Conduct the HIVTSQ(s) at Day 1 pre- dosing; at all other visits conduct post-dosing. Conduct the HIVTSQ(c) at WD ONLY if the subject WD between Week 4 and Week 24. Conduct the HIVMQ post injection.
h) Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and prior to reinitiating injections after > 7 days of treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD. U=Urine S=Serum
i) Plasma for storage samples collected for possible analyses, back-up in case samples are lost or damaged in transit to lab, for geno/pheno analyses and virologic failures.
j) Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k) Take PK samples pre-dose except Week 1 and Week 29 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of GSK744+ABC/3TC+RPV and another sample taken 2 hours after the last injection. S=Sample for storage
l) Subjects should take GSK744+ABC/3TC+RPV on Day 1 in the clinic prior to PK sampling. Day 1 injections will include 2 x GSK744 LA 400 mg + 1 x TMC278 LA 600 mg IM. Thereafter injections are 1 x GSK744 LA 400 mg + 1 TMC278 LA 600 mg IM.
m) Subjects who WD must enter Long-Term Follow Up (see Section 3.2.6) instead of completing the WD visit. If they cannot enter Long-Term Follow-Up complete WD assessments.
n) Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
o) If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting; note time and location of injection (right or left) in eCRF. Dosing is expected to occur within 21-35 days from the previous dose while keeping to the subjects visit schedule projected from Day 1 of the Maintenance Period. **All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**

Time and Events Table – Maintenance Period for Oral Regimen (GSK744+ABC/3TC)

Procedures For Maintenance - oral regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 98 [n]	WD [o]
Verify Eligibility	X																							X [j]	X [k]	X [k]	
Randomization	X																										
Symptom Directed PE and Medical Assessment [a]	X	X	X	X	X	X	X		X		X		X			X			X			X			X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X				X		X				X			X			X			X			X		X
Weight	X						X						X												X		X
ECG [c]	X[pre]	X	X				X		X				X			X			X			X			X		X
HIV Associated Conditions, AE and SAE Assessment, Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Diary [d]	D/R						D/R						D/R												R		R
eC-SSRS [e]	X	X	X	X	X	X	X		X		X		X			X			X			X			X	X	X

Procedures For Maintenance - oral regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 98 [n]	WD [o]
HIVTSQ(s) [e]	Xpre	X	X				X						X												X		X
HIVTSQ(c) [e]							X																				X [e]
HIVMQ [e]			X				X						X												X		X
Chemistry and Hematology	X	X	X	X	X	X	X		X		X		X			X			X			X			X		X
Pregnancy Testing [f]	S	S	S	S	S	S	S		S		S		S			S			S			S			S		S
HIV-1 RNA & sample for storage [g]	X	X	X	X	X	X	X		X		X		X			X			X			X			X		X
CD4+/ CD8+	X	X	X				X		X				X			X			X			X			X		X
Urinalysis and urine microalbumin/ creatinine ratio	X						X						X						X						X		X
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X	X					X						X						X						X		X
PT/PTT/INR	X						X						X												X		X
PK Sample [i]	X						X						X												X		X
Study Treatment Dispensation &	X	X	X	X	X	X	X		X		X		X			X			X			X			X	X Add RPV,	

Procedures For Maintenance - oral regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 98 [n]	WD [o]
Accountability																										[l]	
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [m]	X
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Grey shading indicates visits may be conducted via telephone. The purpose of these visits will be to assess the subject for any AEs, changes to Con Meds, changes to their overall health and any other medical concerns.

D=Day W=Week Pre=Pre-dosing PE = Physical Exam

a. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.
b. .Measure vital signs after about 5 minutes of rest in a semi-supine position.
c. 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, it is preferable to conduct 2 – 4 hours after dosing.
d. D=Dispense R=Review
e. Preferably completed at the beginning of the visit. Conduct the HIVTSQ(s) at Day 1 prior to dosing. Conduct the HIVTSQ(c) at WD ONLY if the subject WD between Week 4 and Week 24.
f. Women of childbearing potential only. S=Serum
g. Plasma for storage samples are collected for possible future analyses, as back- up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures
h. Plasma for storage samples are collected for possible future analyses, as back-up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures
i. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
j. All PK samples should be taken pre-dose within 20-28 hours after the last dose of IP taken. Subjects will take their dose of IP in the clinic at PK visits.
k. Assess subject willingness to continue on to the Extension Period.
l. The results from the Week 96 HIV-1 RNA sample must be <50 c/mL and results available at the time of the Week 98 visit. See Section 3.2.5.2.
m. For subjects eligible to enter the Extension Period Add RPV to current treatment regimen. Subjects will take their Maintenance treatment regimen+RPV until Week 100.
n. Remind subjects of the change in study treatment and visit frequency which begins at Week 100.
o. Only for those subjects electing to transition to GSK744 LA+TMC278 LA.
p. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone

Time and Events Table – Extension Period

Procedures for Extension	W 100	W 104	W 108	W 112	W 116	W 120	W 124	W 128	W 132	W 136	W 140 [a]	W 144 [a]	W 148 [a]	Continue until either locally approved and commercially available, t he subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.	WD [k,l]	Notes ***See footnote "a" for continuation of visit schedule after Week 148.***
Symptom Directed Physical Exam, ISR and Medical Assessment [b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	a. Continue this pattern for visits for the remainder of the study. For example, Week 152 will be conducted just like Week 140. Week 156 will be conducted just like Week 144 and Week 160 will be conducted just like Week 148. b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management. c. Measure vital signs after about 5 minutes of rest in a semi-supine position. d. Can be done at any time during the visit. e. Preferably completed at the beginning of the visit. f. Women of childbearing potential must have a (-) urine pregnancy test prior to any injection and prior to reinitiating injections after > 7 days of treatment interruption. U=Urine g. Plasma for storage samples are collected for possible future analyses, as back-up in case of lost damaged in
Vital Signs (BP, HR) [c]	X			X			X			X			X		X	
Weight	X			X			X			X			X		X	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
12-Lead ECG [d]				X			X			X			X		X	
Columbia Suicide Severity Rating Scale (eC-SSRS) [e]	X	X	X	X			X			X			X		X	
Chemistry and Hematology	X	X	X	X			X			X			X		X	
Pregnancy Testing [f]	U	U	U	U	U	U	U	U	U	U	U	U	U		U	
HIV-1 RNA and sample for storage [g]	X	X	X	X			X			X			X		X	

Procedures for Extension	W 100	W 104	W 108	W 112	W 116	W 120	W 124	W 128	W 132	W 136	W 140 [a]	W 144 [a]	W 148 [a]	Continue until either	WD [k,l]	Notes ***See footnote "a" for continuation of visit schedule after Week 148.***
CD4+	X			X			X			X			X		X	transit to the lab and for geno/pheno analyses for virologic failures.
Urinalysis and urine microalbumin/ creatinine ratio	X			X			X			X			X	Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason	X	h. Fast overnight; minimum of a 6 hour fast is acceptable.
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X			X			X			X			X		X	i. Dispense at each visit. E = Episodic
PT/PTT/INR															X	j. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting; note time and location of injection (right or left) in eCRF. Dosing is expected to occur within 21-35 days from the previous dose while keeping to the subjects visit schedule projected from Day 1 of the Maintenance Period. **All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
ISR Diary Dispensation and Review [i]	E	E	E	E	E	E	E	E	E	E	E	E	E		E review	
Study Treatment Administration [j]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X			k. Or Long-Term Follow Up
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X			l. Follow Up Visit: ~4 weeks after the last dose of IP only if subject has ongoing AEs/lab abnormalities at the last visit.

Time and Events Table – Long-Term Follow Up Period

Procedures for Long-Term Follow Up	Month 1 [a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	Every effort should be made to enter subjects into the Long-Term Follow Up if they withdraw from or discontinue the study after receiving at least one dose of GSK744 LA and / or TMC278 LA. a) The start of the 52-week follow up period begins the day of the last GSK744 LA and/or TMC278 LA dose. b) Women of childbearing potential only. S = Serum c) Fast overnight; however, a minimum of a 6 hour fast is acceptable. d) Women of childbearing potential should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up Period. e) **Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating. This regimen is not provided by the study but the Sponsor will reimburse sites for cost.**
HIV-1 RNA	X	X	X	X	X	X	
CD4+	X	X	X	X	X	X	
Plasma for Storage	X	X	X	X	X	X	
Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [b]	S	S	S	S	S	S	
Urinalysis and urine microalbumin/ creatinine ratio	X				X	X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [c]					X	X	
PT/PTT/INR					X	X	
Contraception Counselling [d]	X	X	X	X	X	X	
HAART Dispensation [e]	X	X	X	X	X	X	

Revised text:

Time and Events Table – Induction Period

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
Written Informed Consent	X							a. Complete all Screening assessments within 28 days. Subjects may be randomized and begin the Induction Period as soon as all Screening assessments are complete. Subjects may be rescreened once and will be assigned a new subject number. b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and / or care. c. Height collected at Baseline only. d. Measure vital signs after about 5 minutes of rest in a semi-supine position. e. Perform ECG at Baseline in triplicate prior to dosing; preferably 2 – 4 hours post dosing for all other visits. f. Collect full routine medical history plus; cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders. g. Collect SAEs at Screen only if associated to study participation.
Demography		X						
Eligibility Verification	X	X				X [h]		
Physical Exam [b]	X							
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X	X and smoking status	
Weight and Height [c]		X					X	
Vital Signs (BP, HR) [d]	X	X				X	X	
12-Lead ECG [e]	X	X pre-dose x3				X	X	
Medical History [f]	X							
Medication History / Prior ART History	X							
CDC Classification	X	X						
HIV Associated Conditions			X	X	X	X	X	

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
AE and SAE Assessment, Con Meds	X [g]	X	X	X	X	X	X	h. Confirmation of eligibility to enter the Maintenance Period. See Section 3.2.3. i. Preferably completed at the beginning of the visit. j. Collect for women of childbearing potential only. A negative urine pregnancy test is required prior to beginning the Induction Period. S=Serum/U=Urine k. Plasma for storage will be used: to determine genotypic eligibility at Screen, for possible future analyses, as back- up in case samples are lost or damaged in transit to the lab and for genotypic and phenotypic analyses in cases of virologic failure. l. Overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable. m. Collect PGx sample at Baseline. May be collected later during the study if necessary.
Columbia Suicide Severity Rating Scale (eC-SSRS) [i]	X	X	X	X	X	X	X	
HIVTSQ(s) [i]			X			X	X	
HIVMQ						X		
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	
Pregnancy Testing [j]	S	U	S	S	S	S	S	
HIV-1 RNA and sample for storage [k]	X	X	X	X	X	X	X	
CD4+ and CD8+	X	X	X	X		X	X	
Urinalysis		X				X	X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [l]		X				X	X	
Hepatitis B (HBsAg) and Hepatitis C (anti-HCV Ab), HLA-B*5701	X							
PT/PTT/INR	X	X						
PGx [m]		X						

Procedures for Induction	Screening Period [a]	Baseline / Week (-20)	Week (-16)	Week (-12)	Week (-8)	Week (-4)	WD	Notes
PK Sample (S)torage							S	n. Instruct subjects to continue to take the Induction regimen (including RPV) through Day 1 of the Maintenance Period. Subjects should be reminded to take the Day 1 dose in the clinic for PK sampling and return the PK diary. The PK diary will be completed by all subjects in case they are randomized to continue on the GSK744 + ABC/3TC arm. o. Remind subjects of the potential change in study treatment and visit frequency beginning at Day 1.
Study Treatment Dispensation		X	X	X	X	X [n] Add RPV		
Study Treatment Accountability (pill counts)			X	X	X	X	X	
PK Diary Dispensation						X [n]		
Subject Visit Reminder Contact	X	X	X	X	X	X [o]	X	
Subject Contact Detail Confirmation	X	X	X	X	X	X		
Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.								

Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA+TMC278 LA Q8W)

Procedures For Maintenance – **Q8W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
Verify Eligibility	X																												
Randomization	X																												
Symptom Directed PE, ISR & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X	X				X			X					X		X		X		X		X		X		X	X
Weight and BMI	X										X					X												X	X
ECG [c]	X[pre]	X	X	X				X			X					X				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Diary (D)aily/(E)pisodic) [d]	D	E	E	E	E	E	E	D	E	E	E	E	D	E	E	E		E		E		E		E		E		E	E
Exercise Habit Assessment [e]		X							X					X															
eC-SSRS [f]	X		X	X	X	X	X	X		X	X		X			X		X		X		X		X		X		X	X

Procedures For Maintenance – **Q8W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
HIVTSQ(s) [g]	X[pre]			X							X					X												X	X
HIVTSQ(c) [g]											X																		X
HIVMQ [g]				X							X					X												X	X [g]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
Pregnancy Test (U)rine/(S)erum [h]	U		U	U	U	U	U	U		U	U	U	U		U	U		U		U		U		U		U		U	S
HIV-1 RNA & sample for storage[i]	X		X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
CD4+/ CD8+	X		X	X				X			X					X		X				X		X				X	X
Urinalysis	X										X					X						X						X	X
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X		X								X					X						X						X	X
PT/PTT/INR	X										X					X												X	X
PK Sample (S)torage [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		S		S		S		S		S		S	S
Study Treatment Administration [m]	X [l]		X	X		X		X			X		X			X		X		X		X		X		X		X[n]	

Procedures For Maintenance – **Q8W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index
Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including injection site reactions.

a) Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject. See Section 6.10.1 for ISR assessment requirements.
b) Measure vital signs after about 5 minutes of rest in a semi-supine position.
c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit.
d) Subjects will complete a (D)aily diary of injection site reactions from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. At all other visits subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.
e) Subject's exercise habits will be assessed daily from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. Assessments will include type and duration of cardiovascular exercise and duration of any strength or other strenuous exercises. This information will be collected via the daily ISR diary and entered into the eCRF.
f) Preferably completed at the beginning of the visit.
g) Conduct the HIVTSQ(s) at Day 1 pre-dosing; at all other visits conduct post-dosing. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ post injection.
h) Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
i) Plasma for storage samples collected for possible analyses, back-up in case samples are lost or damaged in transit to lab, for geno/pheno analyses and virologic failures.
j) Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k) Take PK samples pre-dose except Weeks 1, 12, 20, 25, 28, 36, 41 and 44 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of GSK744+ABC/3TC+RPV. A second Day 1 PK sample will be collected 2 hours after the last injection.
l) Subjects should take GSK744+ABC/3TC+RPV on Day 1 in the clinic prior to PK sampling and injections should be administered within 2 hours of this where possible.
m) Subjects will take final dose of Induction regimen in the clinic at Day 1 and begin injections. Day 1 injections are 2 x GSK744 LA 400 mg IM + 1 x TMC278 LA 900 mg IM. Week 4 injection is 1 x GSK744 LA 600 mg IM (no TMC278 LA). At Week 8 and Q8W, injections are 1 x GSK744 LA 600 mg IM + 1 x TMC278 LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
n) Subjects will receive the selected Extension dosing regimen (either Q8W or Q4W) at this visit. If switching to Q4W, injections are 1 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. Subjects may immediately begin the new regimen at Week 96.
o) Remind subjects of the potential change in study treatment and visit frequency beginning at Week 96.
p) Subjects who WD must enter Long-Term Follow Up (see Section 3.2.6) instead of completing the WD visit. If they cannot enter Long-Term Follow-Up complete WD and Follow Up assessments.
q) Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required for subjects not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by phone.

Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA+TMC278 LA Q4W)

Procedures For Maintenance – **Q4W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
Verify Eligibility	X																												
Randomization	X																												
Symptom Directed PE, ISR & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X	X				X			X					X		X		X		X		X		X		X	X
Weight and BMI	X										X					X												X	X
ECG [c]	X[pre]	X	X	X				X			X					X				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Diary (D)aily/(E)pisodic) [d]	D	E	E	E	E	E	E	D	E	E	E	E	D	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
Exercise Habit Assessment [e]		X							X					X															
eC-SSRS [f]	X		X	X	X	X	X	X		X	X		X			X		X		X		X		X		X		X	X

Procedures For Maintenance – **Q4W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
HIVTSQ(s) [g]	X[pre]			X							X					X												X	X
HIVTSQ(c) [g]											X																		X
HIVMQ [g]				X							X					X												X	X [g]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
Pregnancy Test (U)rine/(S)erum [h]	U		U	U	U	U	U	U		U	U	U	U		U	U	U	U	U	U	U	U	U	U	U	U	U	U	S
HIV-1 RNA & sample for storage[i]	X		X	X	X	X	X	X		X	X	X	X		X	X		X		X		X		X		X		X	X
CD4+/ CD8+	X		X	X				X			X					X		X				X		X				X	X
Urinalysis	X										X					X						X						X	X
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X		X								X					X						X						X	X
PT/PTT/INR	X										X					X												X	X
PK Sample (S)torage [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		S		S		S		S		S		S	S
Study Treatment Administration [m]	X [l]		X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	

Procedures For Maintenance – **Q4W** regimen	D1	W 1	W 4	W 8	W 12	W 16	W 20	W 24	W 25	W 28	W 32	W 36	W 40	W 41	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p, q]
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index

a) Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject. See Section 6.10.1 for ISR assessment requirements.

b) Measure vital signs after about 5 minutes of rest in a semi-supine position.

c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit.

d) Subjects will complete a (D)aily diary of injection site reactions from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. At all other visits subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.

e) Subject's exercise habits will be assessed daily from Day 1 to Week 1, from Week 24 to Week 25 and again from Week 40 to Week 41. Assessments will include type and duration of cardiovascular exercise and duration of any strength or other strenuous exercises. This information will be collected via the daily ISR diary and entered into the eCRF.

f) Preferably completed at the beginning of the visit.

g) Conduct the HIVTSQ(s) at Day 1 pre-dosing; at all other visits conduct post-dosing. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ post injection.

h) Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.

i) Plasma for storage samples collected for possible analyses, back-up in case samples are lost or damaged in transit to lab, for geno/pheno analyses and virologic failures.

j) Fast overnight; however, a minimum of a 6 hour fast is acceptable.

k) Take PK samples pre-dose except Week 1, Week 25 and Week 41 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of GSK744+ABC/3TC+RPV. A second Day 1 PK sample will be collected 2 hours after the last injection.

l) Subjects should take GSK744+ABC/3TC+RPV on Day 1 in the clinic prior to PK sampling and injections should be administered within 2 hours of this where possible.

m) Subjects will take final dose of Induction regimen in the clinic at Day 1 and begin injections. Day 1 injections are 2 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. At Week 4 and Q4W, injections are 1 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**

n) Subjects will receive the selected Extension dosing regimen (either Q8W or Q4W) at this visit. If switching to Q8W, no loading dose is necessary. Injections are 1 x GSK744 LA 600 mg IM + 1 x TMC278 LA 900 mg IM.

o) Remind subjects of the potential change in study treatment and visit frequency beginning at Week 96.

p) Subjects who WD must enter Long-Term Follow Up (see Section 3.2.6) instead of completing the WD visit. If they cannot enter Long-Term Follow-Up complete WD and Follow Up assessments.

q) Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required for subjects not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by phone.

Time and Events Table – Maintenance Period for Oral Regimen (GSK744+ABC/3TC)

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
Verify Eligibility	X																								X [l]		X [l, n]		
Randomization	X																												
Symptom Directed PE & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X				X		X				X		X		X		X		X		X		X	X	X	X	X
Weight and BMI [c]	X								X				X												X			X	X
ECG [d]	X pre	X	X				X		X				X		X		X		X		X		X		X			X pre	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Diary (D)ispensation and (R)eview [e]	R							D	R			D	R																
eC-SSRS [f]	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X				X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
HIVTSQ(s) [g]	X pre		X						X				X												X				X
HIVTSQ(c) [g]									X																				X
HIVMQ [g]			X						X				X												X				X [g]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X	X
Pregnancy Test (S)erum/(U)rine [h]	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S		S		S		S		S	S	S	U	S
HIV-1 RNA & sample for storage [i]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X [n]	X	X	X
CD4+/ CD8+	X	X	X				X		X				X		X				X		X				X		X	X	X
Urinalysis	X								X				X						X						X			X	X
Fasting: Glucose, Insulin, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X	X							X				X						X						X			X	X
PT/PTT/INR	X								X				X												X			X	X
PK Sample [k]	X								X				X												S			S	X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
Study Treatment Dispensation and Accountability [o]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X[m]	X	X Add RPV	X Add injection	
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [p]	X[m,p]	X [p]	X [p]	X [p]	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index
Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including compliance.

a. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.
b. Measure vital signs after about 5 minutes of rest in a semi-supine position.
c. BMI collected at Week 104 only.
d. 12-Lead ECG – Conduct pre-dose at Day 1 and Week 104. At all other visits, it is preferable to conduct 2 – 4 hours after dosing.
e. Review PK diary at the beginning of the visit to verify time of last dose. PK samples must be collected within the window of 20-28 hours after the last dose taken. Contact the study team for guidance in cases when subject's last dose is not within window. Visit may need to be rescheduled.
f. Preferably completed at the beginning of the visit.
g. Conduct the HIVTSQ(s) at Day 1 prior to dosing and post dosing where possible at all other visits. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ preferably at the beginning of the visit, but may be completed at any time during the visit.
h. Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
i. Plasma for storage samples are collected for possible future analyses, as back- up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures
j. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k. All PK samples should be taken pre-dose within 20-28 hours after the last dose of IP taken. Subjects will take their dose of IP in the clinic at PK visits. S=Storage
l. Assess subject's willingness to continue on to the Extension Period. If not continuing into the Extension Period, this is the subject's last study visit.
m. For subjects continuing into the Extension Period only.
n. The Week 100 HIV-1 RNA result must be <50 c/mL to be eligible to continue into the Extension Period. See Section 3.2.5.2. Subjects ineligible for Extension will end their study participation at Week 102 (no withdrawal visit needed).
o. Subjects will discontinue RPV at Day 1 and begin taking 1 x GSK744 + 1 x ABC/3TC tablet once daily. At Week 96 and Week 100, while awaiting eligibility for Extension, subjects will continue their GSK744+ABC/3TC regimen. At Week 102, subjects eligible to enter the Extension Period will add once daily RPV to their GSK744+ABC/3TC regimen and continue to take GSK744+ABC/3TC +RPV once daily through Week 104. At Week 104, subjects will take final dose of GSK744+ABC/3TC+RPV in the clinic and begin the selected IM regimen (Q8W or Q4W). See Section 5.1.6 for IM dosing administration as loading doses are required.
p. Remind subjects of the change in study and assessments for eligibility into Extension.
q. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.

Time and Events Table – Extension Period if Q8W is Selected

Procedures for Extension if Q8W is Selected	W 104 [a]	W 108[b] From Oral Arm Only	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184 [c]	W 192 [c]	W 200 [c]	WD [n, o]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "b" for continuation of visit schedule after Week 200. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [e]	X		X		X		X		X		X		X		X	a. Subjects switching from the oral regimen will complete Week 104 visit as per the Maintenance T&E Section 6.4.
Weight & BMI	X		X		X		X		X		X		X		X	b. Week 108 visit is only for subjects switching from the oral arm.
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	c. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 184, Week 216 will be conducted just like Week 192 and Week 224 will be conducted just like Week 200.
12-Lead ECG [f]	X	X	X		X		X		X		X		X		X	d. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
Clinical Chemistry and Hematology	X	X	X		X		X		X		X		X		X	e. Measure vital signs after about 5 minutes of rest in a semi-supine position.
Pregnancy Testing (U)rine [g]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	f. Can be done at any time during the visit. g. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD.

Procedures for Extension if Q8W is Selected	W 104 [a]	W 108[b] From Oral Arm Only	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184 [c]	W 192 [c]	W 200 [c]	WD [n, o]	Notes
HIV-1 RNA and sample for storage [h]	X		X		X		X		X		X		X		X	h. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures. i. Fast overnight; minimum of a 6 hour fast is acceptable. j. Samples should be collected pre-dose. k. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. l. Q8W Injections are 1 x GSK744 LA 600 mg IM + 1 x TMC278 LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.** m. Subjects switching from the oral arm will receive their 2nd loading dose injection of 1 x GSK744 LA 600 mg (no TMC278 LA).
CD4+	X		X		X		X		X		X		X		X	
Urinalysis	X		X		X		X		X		X		X		X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [i]	X		X		X		X		X		X		X		X	
PT/PTT/INR															X	
PK Sample (S)torage [j]	S		S		S		S		S		S		S		S	
ISR Diary Dispensation [k]	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E review	
Study Treatment Administration [l]	X [a]	X [m]	X	X	X	X	X	X	X	X	X	X	X	X		

Procedures for Extension if Q8W is Selected	W 104 [a]	W 108[b] From Oral Arm Only	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184 [c]	W 192 [c]	W 200 [c]	WD [n, o]	Notes
																n. Or Long-Term Follow Up o. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Time and Events Table – Extension Period if Q4W is Selected

Procedures for Extension if Q4W is Selected	W 100 [a]	W 104 [a]	W 108	W 112	W 116	W 120	W 124	W 128 [b]	W 132 [b]	W 136 [b]	W 140 [b]	WD [l, m]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "b" for continuation of visit schedule after Week 140. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [d]	X		X				X				X	X	a. Subjects switching from the oral regimen will complete Week 100 and 104 visits as per the Maintenance T&E Section 6.4.
Weight & BMI	X		X				X				X	X	b. Continue this pattern for visits for the remainder of the study. For example, Week 144 will be conducted just like Week 128, Week 148 will be conducted just like Week 132, Week 152 will be conducted just like Week 136 and Week 156 will be conducted just like Week 140.
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	c. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
12-Lead ECG [e]	X		X				X				X	X	d. Measure vital signs after about 5 minutes of rest in a semi-supine position.
Clinical Chemistry and Hematology	X	X	X				X				X	X	e. Can be done at any time during the visit.
Pregnancy Testing (U)rine [f]	U	U	U	U	U	U	U	U	U	U	U	U	f. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD.
HIV-1 RNA and sample for storage [g]	X	X	X				X				X	X	g. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
CD4+	X	X	X				X				X	X	

Procedures for Extension if Q4W is Selected	W 100 [a]	W 104 [a]	W 108	W 112	W 116	W 120	W 124	W 128 [b]	W 132 [b]	W 136 [b]	W 140 [b]	WD [l, m]	Notes
Urinalysis	X		X				X				X	X	h. Fast overnight; minimum of a 6 hour fast is acceptable. i. Samples should be collected pre-dose. j. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. k. Q4W Injections are 1 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.** l. Or Long-Term Follow Up m. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X		X				X				X	X	
PT/PTT/INR												X	
PK Sample (S)torage [i]	S	S	S				S				S	S	
ISR Diary Dispensation [j]	E	E	E	E	E	E	E	E	E	E	E	E review	
Study Treatment Administration [k]	X [a]	X [a]	X	X	X	X	X	X	X	X	X		
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X		
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X		

Time and Events Table – Long-Term Follow Up Period

Procedures for Long-Term Follow Up	Month 1 [a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	Every effort should be made to enter subjects into the Long-Term Follow Up if they withdraw from or discontinue the study after receiving at least one dose of GSK744 LA and / or TMC278 LA. a) The start of the 52-week follow up period begins the day of the last GSK744 LA and/or TMC278 LA dose. b) Women of childbearing potential only. S = Serum c) Fast overnight; however, a minimum of a 6 hour fast is acceptable. d) Women of childbearing potential should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up Period. e) **Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating. This regimen is not provided by the study but the Sponsor will reimburse sites for cost.**
HIV-1 RNA	X	X	X	X	X	X	
CD4+	X	X	X	X	X	X	
Plasma for Storage	X	X	X	X	X	X	
PK Sample for Storage	X	X	X	X	X	X	
Clinical Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [b]	S	S	S	S	S	S	
Urinalysis	X				X	X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides					X	X	
PT/PTT/INR					X	X	
Contraception Counselling [d]	X	X	X	X	X	X	
HAART Dispensation [e]	X	X	X	X	X	X	

Section 6.8.1 – Screening

Revised to (changes struck through and underlined).

All clinical and laboratory assessments of eligibility must be performed and reviewed within 28 days of initiating the Screening process. All Screening results must be available prior to randomization.

Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the first Induction Period visit prior to enrollment.

Subjects may ~~be randomized~~enroll and begin the Induction Period as soon as all Screening assessments are complete and the results are available and documented.

Each subject screened ~~Subjects who meet all entry criteria are randomized and~~will be assigned a ~~randomization~~subject number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new subject number. Subjects who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

At Screening, samples for HIV-1 genotypic and phenotypic resistance testing and plasma HIV-1 RNA measurement will be obtained.

~~*Known* moderate or severe hepatic impairment (Class B or C) is exclusionary. Child-Pugh classification will be assessed at the Screening visit in subjects with a concern for hepatic impairment (see Section 11.2).~~

Section 6.8.2 – Baseline

Revised to (changes struck through and underlined).

Subjects will have "Baseline" assessments completed at ~~either Week (-24) or Week (-16) depending on the length of~~ the beginning of the Induction Period~~in which they were randomized.~~

Any changes to the eligibility parameters must be assessed and any results required must be available and reviewed prior to ~~randomization~~ enrollment (e.g. urine pregnancy test for women of child bearing potential).

HIV-1 genotypic resistance testing and plasma HIV-1 RNA measurement results from Screening must be available prior to the Baseline visit.

Section 6.9.3 - HIV Associated Conditions

Revised to (changes underlined).

HIV-associated conditions will be recorded as per Time and Events schedule (Section 6). HIV-associated conditions will be assessed according to the 1993 CDC Revised

Classification System for HIV Infection in Adults (see Section 11.1). Indicators of clinical disease progression are defined as:

CDC Category A at enrollment → Category B event;

CDC Category A at enrollment → Category C event;

CDC Category B at enrollment → Category C event;

CDC Category C at enrollment → New Category C Event;

CDC Category A, B or C at enrollment → Death.

Section 6.10.1 - Clinical evaluations

Revised to (changes struck through and underlined).

The following clinical evaluations will be performed according to the Time and Events schedule (see Section 6):

- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of GSK744 LA or TMC278 LA or ~~prior to reinitiating therapy after an interruption of GSK744 LA or TMC278 LA > 7 day~~ as required by the medical monitor following a treatment interruption(s).
- Injection Site Reactions (ISRs) will be assessed for the following clinically as well as patient-reported by utilizing a subject diary:
  - Daily from Day 1 – 7, from Week 24 – Week 25 and again daily from Week ~~28~~40 to Week ~~29~~41: Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).

Section 6.10.2 – Laboratory Assessments

Removed collection of Phosphate (inorganic phosphorus) and changed reporting of Creatinine clearance and CD8+ cells from Week 24 to Week 32.

Section 6.10.3 - Liver Chemistry Stopping Criteria

Revised to (changes struck through and underlined).

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the follow-up period. IP will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin, bilirubin fractionation required).

NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a

subject meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria.

- ALT ≥8xULN.
- ALT ≥3xULN (if Baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x Baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ~~ALT ≥3xULN with acute hepatitis symptoms or hypersensitivity if Baseline ALT≤ULN OR ALT ≥3 fold increase from Baseline with acute hepatitis symptoms or hypersensitivity if Baseline ALT>ULN.~~
- ALT ≥5xULN and <8xULN that persists ≥2 weeks (with bilirubin <2 ULN & no signs or symptoms of acute hepatitis or hypersensitivity).
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, sites should **evaluate the presence of detectable urinary bilirubin on dipstick**, which indicates direct bilirubin elevations and suggests liver injury.

Liver Chemistry Stopping Criteria, Subject Management

Subjects who develop ALT ≥5xULN must be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When any of the liver chemistry stopping critera is met, do the following:

- Immediately hold IP.
- Report the event to the medical monitor within 24 hours of learning its occurrence (Section 6.10.13, Section 6.10.15).
- Complete the liver event eCRF and SAE eCRF, where applicable, (see Section 6.10.13).
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (described below), and monitor the subject until liver chemistries resolve, stabilize, or return to Baseline values as described below.
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.

- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within Baseline values.

Make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - HBsAg and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test). The site must contact GSK when this test is required. Please refer to the Quest Laboratory Manual.
- ~~Hepatitis E IgM antibody;~~
- Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant

medications report form. Record alcohol use on the liver event alcohol intake case report form.

Liver Chemistry Stopping Criteria - Rechallenge

Subjects who meet liver toxicity stopping criteria should not be retreated with investigational product unless an exemption has been approved by the ViiV Safety and Labeling Committee (VSLC). The guideline for Rechallenge/Restart approved by the VSLC, which is maintained as a separate document (See Section 11.4, Appendix 4), must be followed.

Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by the VSLC for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may **resume as per protocol.**

Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by the VSLC for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.

- Study drug must be administered at the dose specified by the VSLC.

Subjects approved by the VSLC for restarting IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

See Section 11.4, Appendix 4 for further details.

Section 6.10.6.1 - Treatment Interruption Due to an Adverse Event

Revised to (changes struck through and underlined).

No toxicity-related dose reductions of IP will be allowed. IP and background NRTIs should be restarted as soon as medically appropriate; in general, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of IP or temporary interruption of one or more but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Any interruption in therapy during the Maintenance Period, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the medical monitor prior to resumption of therapy. The medical monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval (Section 5.7). **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred.** Any interruption outside of this guidance MUST be discussed with the medical monitor prior to reinitiating IM IP (see Section 5.7.2).

Section 6.10.11 - Injection Site Reaction Monitoring

Revised to (changes struck through and underlined).

Subjects on either IM regimen will be monitored closely both clinically and by patient report for the following in relation to injection site reactions:

- Pain, tenderness, pruritis, warmth, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).

Digital photographs will be documented where possible on all subjects who have an injection site reaction that is ~~are~~either serious or Grade 2 or above that persist beyond 2 weeks. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Section 6.10.12.1 - Pregnancy Testing

Women of childbearing potential must have a negative pregnancy test at Screening, the first Induction Period visit and prior to administration of each GSK744 LA and / or TMC278 LA injection. Pregnancy testing will also be conducted as per the Time and Events Table (see Section 6) and at anytime during the trial when pregnancy is suspected.

Additionally, the medical monitor may request that a pregnancy test ~~should also~~ be performed in the event of a treatment interruption greater than 7 days. ~~A negative test result is required to reinitiate GSK744 LA and / or TMC278 LA.~~

Section 6.11 – Pharmacokinetics

Original text:

Plasma samples for determination of GSK744 and TMC278 concentration will be collected throughout the study. Samples for determination of RPV will be protected from light until analyzed.

PK Sample Collection

Blood samples for evaluation of GSK744 (2mL each) and TMC278 (3mL each) plasma PK will be collected from all subjects randomized to receive GSK744 LA + TMC278 LA for determination of GSK744 and TMC278 concentrations as described in Table 4. All PK samples will be collected prior to LA dosing, except at Weeks 1 and 29 which may be collected anytime during the Week 1 and Week 29 visits, respectively. The exact date and time of the PK sample should be recorded in CRF.

For subjects randomized to GSK744, pre-dose samples will be collected as described in Table 4. These samples must be collected within the window of 20-28 hours after the last dose taken. Subjects will be expected to complete a PK dosing diary card noting the date and time of the last three doses of IP prior to the scheduled clinic visits on Day 1, Weeks 24, 48 and 96. The information from the diary card will be recorded in the eCRF. Additionally, dosing information on the clinic day, including whether or not the dose was administered with food, and the actual date and time of the PK samples, must be recorded on the CRF. Subjects will take their dose of oral IP in the clinic at PK visits.

Table 4 GSK744 and TMC278 Plasma Pharmacokinetic Sample Schedule

Group	Analyte	Week	Sample Times Relative to Dose
LA	GSK744	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 28, 29, 32, 36, 40, 44 and 48	Pre-Dose: Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1 1 Week Post Dose: Weeks 1, 29
	TMC278	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 28, 29, 32, 36, 40, 44 and 48	Pre-Dose: Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1 1 Week Post Dose: Weeks 1, 29
Oral (Control Arm only)	GSK744	Day 1, Weeks: 24, 48 and 96	Pre-Dose: Day 1, Weeks 24, 48 and 96

Additional GSK744 and TMC278 PK samples for storage will be collected at Weeks 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 and 96 for subjects on GSK744 LA+TMC278 LA and at Months 1, 3, 6, 9 and 12 for subjects in the Long-Term Follow Up Period. These samples may be analyzed in case of protocol-defined virologic failure or to investigate any PK related issues (such as missing dose, missing sample, suspected non-adherence etc.).

Revised text:

Plasma samples for determination of GSK1265744 and TMC278 concentration will be collected throughout the Maintenance Period of the study. Additional samples will be collected for storage during the Extension and Long-Term Follow Up Period. Samples for determination of RPV will be protected from light until analyzed.

PK Sample Collection

Blood samples for evaluation of GSK1265744 (2mL each) and TMC278 (3mL each) plasma PK will be collected from all subjects randomized to receive GSK744 LA + TMC278 LA for determination of GSK1265744 and TMC278 concentrations as described in Table 4. All PK samples will be collected prior to IM dosing and may be collected at anytime during visits that study treatment is not administered. The exact date and time of the PK sample should be recorded in eCRF.

For subjects randomized to GSK744, pre-dose blood samples for evaluation of GSK1265744 (2mL each) and TMC278 (3mL each) will be collected as described in Table 4. These samples must be collected within the window of 20-28 hours after the last

dose taken. Subjects will be expected to complete a PK dosing diary card noting the date and time of the last three doses of IP prior to the scheduled clinic visits on Day 1, Weeks 32 and 48. The information from the diary card will be recorded in the eCRF. Additionally, dosing information on the clinic day, including whether or not the dose was administered with food, if the subject vomited within 4 hours of dosing and the actual date and time of the PK samples, must be recorded on the eCRF. Subjects will take their dose of oral IP in the clinic at PK visits.

Table 13 GSK744 and TMC278 Plasma Pharmacokinetic Sample Schedule

Group	Analyte	Week	Sample Times Relative to Dose
IM	GSK744	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40 and 48 Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1 1 Week Post Dose: Week 1, Week 25 and Week 41 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
	TMC278	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40 and 48 Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1 1 Week Post Dose: Week 1, Week 25 and Week 41 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
Oral (Control Arm only)	GSK744	Day 1, Weeks: 32 and 48	Pre-Dose: Day 1, Weeks 32 and 48

Additional GSK1265744 and TMC278 PK samples for storage will be collected pre-dose at Weeks 56,64, 72, 80, and 96 for subjects on GSK744 LA+TMC278 LA as per the Time and Events Table (see Section 6.2 and Section 6.3) and in the Extension Period (see Section 6.5 and Section 6.6). Samples for storage will be also be collected at Week 96 and 104 for subjects on GSK744+ABC/3TC and at Months 1, 3, 6, 9 and 12 for subjects in the Long-Term Follow Up Period. These samples may be analyzed in case of protocol-defined virologic failure or to investigate any PK related issues (such as missing dose, missing sample, suspected non-adherence etc.).

Section 6.14 – Health Outcomes

Revised to (changes struck through and underlined).

The HIVTSQ(s) will be administered at the following time points:

- Induction: Week ~~-20~~ (-16) ~~in the 24 Week Induction Period and Week -12 in the 16 Week Induction Period~~ and Week (-4) (pre-dose if possible) ~~in both Induction Periods~~
- Maintenance: pre-dose at Day 1~~and post-dose at Week 4~~, and post-dose (where possible in oral dosing arm) Week 8, Week 32~~24~~, Week 48 and Week 96
- Withdrawal

The HIVTSQ(c) will be administered at the following time points:

- Maintenance: Week 32

The HIVTSQ(c, WD) will be administered at the following time points:

- Withdrawal for subjects withdrawn between Week 8 and Week 32

HIVMQ will be administered at the following time points:

- Induction: Week (-4)
- Maintenance: Week 8, Week ~~24~~ 32, Week 48, Week 96 & Withdrawal
    - IM Regimen: Complete post-injection
    - Oral Regimen: Preferably completed at the beginning of the visit, but may be completed at any time during the visit

Section 8.1 – Hypotheses

Revised to (changes struck through and underlined).

The study is designed to evaluate the efficacy and safety of~~a two-drug regimen consisting of GSK744 LA + TMC278 LA when both are administered as intramuscular injections every 4 weeks~~GSK744 LA 400 mg IM plus TMC278 LA 600 mg IM every 4 weeks and GSK744 LA 600 mg IM plus TMC278 LA 900 mg IM every 8 weeks, relative to GSK744 30 mg once daily plus ABC/3TC once daily, through Week ~~24~~ 32 of the Maintenance Period.

Section 8.2 - Sample Size Assumptions

Original text:

LA treatment relative to Oral treatment

The sample size of 50 subjects per arm and 100 subjects combined in LA arms were chosen to ensure a high probability that a long-acting two drug treatment with truly poor response relative to GSK744 once daily plus NRTIs once daily will not be studied further, while allowing for formal considerations of other factors should efficacy be similar between the treatment arms.

The study is designed to test the comparability of GSK744 LA plus TMC278 LA two-drug regimen to GSK744 30 mg once daily plus ABC/3TC. The primary comparison of interest will be performed using a Bayesian probability model. If the posterior probability that the difference is greater than -10% is large (i.e., ≥90%), then sufficient statistical evidence has been provided for the positive outcome. A response rate of 85% in the GSK744 LA plus TMC278 LA two-drug regimen (compared with an GSK744 plus ABC/3TC response rate of 95%) would result in a rejection of the null hypothesis with a probability of approximately 0.068 (type I error). The given sample size is unlikely to select a random sample that would falsely conclude that GSK744 LA plus TMC278 LA two-drug regimen is comparable with GSK744 plus ABC/3TC if the response rates are truly 85% versus 95%, respectively. If the GSK744 LA plus TMC278 LA two-drug regimen yields an response rate of greater than 92%, then there is a high probability of rejecting the null hypothesis and correctly concluding that GSK744 LA plus TMC278 LA two-drug regimen is at least as good as GSK744 plus ABC/3TC.

Historical response rates of dolutegravir, an integrase compound similar to GSK744, were used as reference for the oral control arm. Response rates for dolutegravir plus ABC/3TC ranged from 93% to 96% at Week 48 in studies SPRING-1, SPRING-2 and SINGLE among subjects who were suppressed (HIV-1 viral load <50 c/mL) at Week 24.

The probability of a positive outcome assuming the true response rate for GSK744 LA plus TMC278 LA two-drug regimen is presented in Table 5.

Table 5 Probability of Positive Outcome Assuming True Response Rates of LA

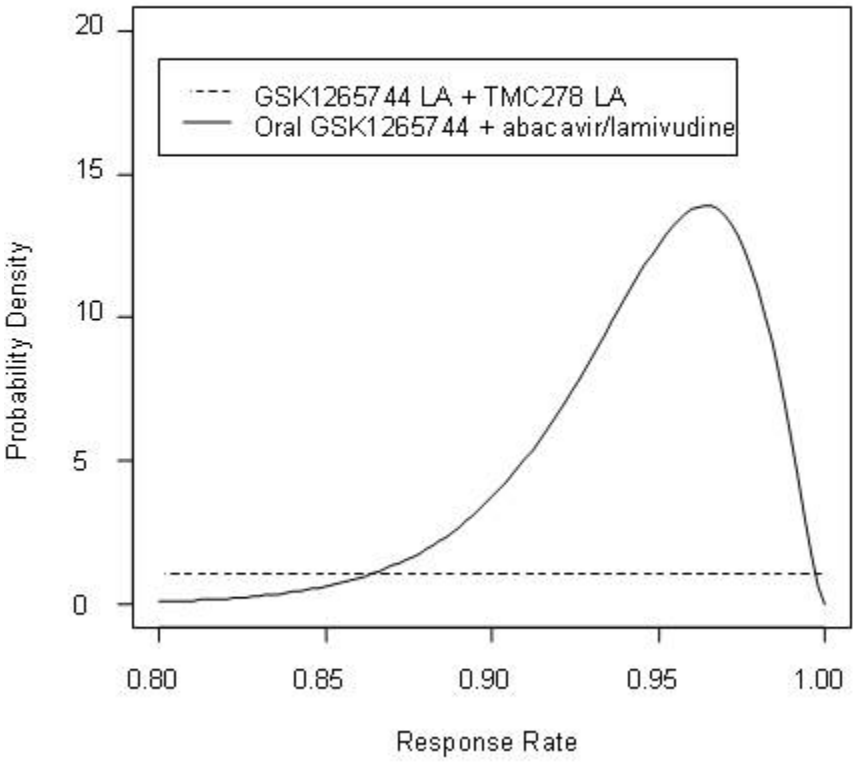
True Response Rate for GSK744 LA plus TMC278 LA two-drug regimen	80%	83%	85%[a]	86%	89%	92%	95%	98%
Probability of Positive Outcome[b]	0.4%	2.5%	6.8%	11%	34%	71%	96%	100%

a. Type I error is <10%.
b. It is assumed that the response rate for GSK744 plus ABC/3TC is 95%.

Incorporation of prior beliefs and information about population parameters is a required part of any Bayesian probability model. The assumptions made will help provide a more reliable estimate when the prior beliefs are combined with the observed data than the data alone as long as the beliefs are reasonable. Therefore, the trial will utilize a Beta (44, 2.6) distribution with the median response rate being 95%, with 99th percentile of 99% and 5th percentile of 88%.

Furthermore, a non- informative prior belief is assumed for the response rate for GSK744 LA plus TMC278 LA two-drug regimen. Therefore, the trial will conservatively utilize a Beta (1, 1) distribution. These priors are displayed in Figure 5

Figure 5 Plot of Prior Distribution for Response Rate for GSK744 LA plus TMC278 LA two-drug regimen and GSK744 plus ABC/3TC



Revised text:

IM treatment relative to Oral treatment

The sample size of 45 subjects in the oral treatment arm and 90 subjects each in the IM treatment arms were chosen to ensure a high probability that a long-acting two drug treatment with truly poor response relative to GSK744 once daily plus ABC/3TC once daily will not be studied further, while allowing for formal considerations of other factors should efficacy be similar between the treatment arms. It is assumed that 85% subjects enrolled will be suppressed at Week (-16), approximately 265 subjects will be enrolled in order to have 225 subjects randomized at Day 1.

The study is designed to test the comparability of GSK744 LA plus TMC278 LA two-drug regimen to GSK744 30 mg once daily plus ABC/3TC. The primary comparison of interest will be performed using a Bayesian probability model. If the posterior probability that the difference is greater than -10% is large (i.e., ≥90%), then sufficient statistical evidence has been provided for the positive outcome. A response rate of 82% in the GSK744 LA plus TMC278 LA two-drug regimen (compared with an GSK744 plus ABC/3TC response rate of 92%) would result in a rejection of the null hypothesis with a probability of approximately 0.064 (type I error). The given sample size is unlikely to

select a random sample that would falsely conclude that GSK744 LA plus TMC278 LA two-drug regimen is comparable with GSK744 plus ABC/3TC if the response rates are truly 82% versus 92%, respectively. If the GSK744 LA plus TMC278 LA two-drug regimen yields an response rate of greater than 92%, then there is a high probability of rejecting the null hypothesis and correctly concluding that GSK744 LA plus TMC278 LA two-drug regimen is at least as good as GSK744 plus ABC/3TC.

Historical response rates of dolutegravir, an integrase compound similar to GSK744, were used as reference for the oral control arm. Response rates for dolutegravir plus ABC/3TC ranged from 92% to 94% at Week 60 in studies SPRING-1, SPRING-2 and SINGLE among subjects who were suppressed (HIV-1 viral load <50 c/mL) at Week 24.

The probability of a positive outcome assuming the true response rate for GSK744 LA plus TMC278 LA two-drug regimen is presented in Table 5.

Table 5 Probability of Positive Outcome Assuming True Response Rates of GSK744 LA plus TMC278 LA

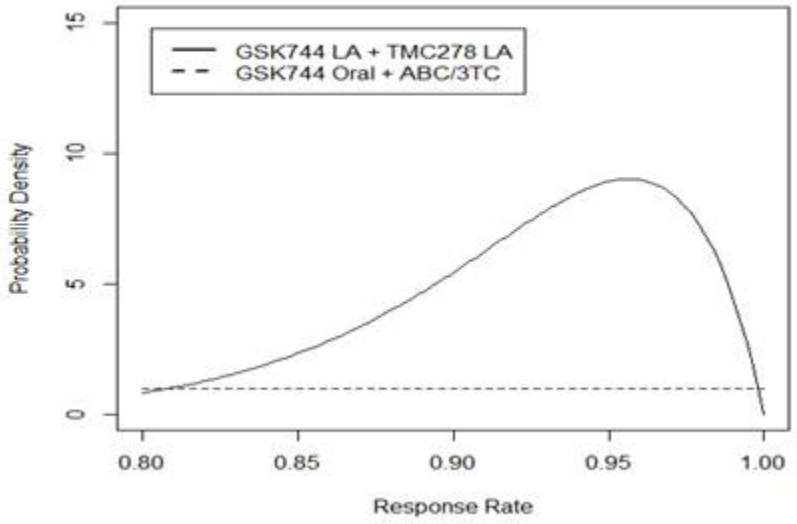
True Response Rate for GSK744 LA plus TMC278 LA two-drug regimen (Q4W or Q8W)	80%	82%[a]	86%	90%	92%	94%	96%
Probability of Positive Outcome[b]	2.8%	6.4%	26%	63%	82%	95%	99%

a. Type I error is <10%.
b. It is assumed that the response rate for GSK744 plus ABC/3TC is 92%.

Incorporation of prior beliefs and information about population parameters is a required part of any Bayesian probability model. The assumptions made will help provide a more reliable estimate when the prior beliefs are combined with the observed data than the data alone as long as the beliefs are reasonable. Therefore, the trial will utilize a Beta (23, 2) distribution with the mean response rate being 92%, with 97.5th percentile of 99% and 2.5th percentile of 78%.

Furthermore, a non- informative prior belief is assumed for the response rate for GSK744 LA plus TMC278 LA two-drug regimen. Therefore, the trial will conservatively utilize a Beta (1, 1) distribution. These priors are displayed in Figure 6.

Figure 6 Plot of Prior Distribution for Response Rate for GSK744 LA plus TMC278 LA two-drug regimen and GSK744 plus ABC/3TC



Section 8.2.2 – Sample Size Sensitivity

Removed:

~~If sample size of LA arm decrease to 50 subjects in the event that the two induction length arms cannot be combined, the likelihood of establishing comparability is reduced.~~

~~With the smaller sample size, if GSK744 LA plus TMC278 LA two-drug regimen yields a response rate of 95%, there would be an 81% probability of rejecting the null hypothesis, as compared with a 96% probability with the selected sample size.~~

Section 8.3.1 - Analysis Populations

Original text:

The following populations will be assessed:

Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all randomized subjects who received at least one dose of IP. Subjects will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the ITT-E population will be the primary population for efficacy analyses.

Intent-to-Treat Maintenance Exposed Population (ITT-ME)

The ITT-ME population consists of all randomized who received at least one dose of IP during the Maintenance Period of the study. Subjects will be analyzed according to the

randomized treatment regardless of what treatment was actually received. The ITT-ME population will be the secondary population for some efficacy analyses.

Per Protocol Population (PP)

This population will consist of subjects in the ITT-E population with the exception of major protocol violators (these will be defined in the RAP of this study). The PP population will be a secondary population for efficacy purposes.

Per Protocol Maintenance Population (PP-M)

This population will consist of subjects in the ITT-ME population with the exception of major protocol violators (these will be defined in the RAP of this study). The PP-M population will be a secondary population for efficacy purposes.

PK Population

The PK Population will include all subjects who received GSK1265744 and / or TMC278 and undergo PK sampling during the study, and provide evaluable GSK1265744 and /or TMC278 plasma concentration data. Subjects in this population will be included in the PK analysis.

Safety Population

The Safety Population consists of all enrolled subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not having consumed any amount of investigational product. Subjects will be analyzed according to the actual treatments received. Subjects will not be excluded from this population as a result of changes to the background regimen. The safety population will be the primary population for safety analyses. All safety analyses will be produced using the safety population.

Maintenance Safety Population

The Maintenance Safety Population consists of all randomized subjects who were exposed to investigational products during the Maintenance Period of the study with the exception of any subjects with documented evidence of not having consumed or been administered any amount of investigational product during the Maintenance Period of the study. Subjects will be analyzed according to the actual treatments received. Subjects will not be excluded from this population as a result of changes to the background regimen. The maintenance safety population will be an additional population for safety analyses.

Revised text:

The following populations will be assessed:

Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all enrolled subjects who received at least one dose of IP. Subjects will be analyzed according to their randomized treatment regardless of what treatment was actually received. Those that are not randomized will be summarized together under a 'Not Randomized' category. The ITT-E population will be the secondary population for some efficacy analyses.

Intent-to-Treat Maintenance Exposed Population (ITT-ME)

The ITT-ME population consists of all randomized who received at least one dose of IP during the Maintenance Period of the study. Subjects will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the ITT-ME population will be the primary population for efficacy analyses.

Per Protocol Maintenance Population (PP-M)

This population will consist of subjects in the ITT-ME population with the exception of major protocol violators (these will be defined in the RAP of this study). The PP-M population will be a secondary population for efficacy purposes.

PK Population

The PK Population will include all subjects who received GSK1265744 and / or TMC278 and undergo PK sampling during the study, and provide evaluable GSK1265744 and /or TMC278 plasma concentration data. Subjects in this population will be included in the PK analysis.

Safety Population

The Safety Population consists of all enrolled subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not having consumed any amount of investigational product. Subjects will be analyzed according to the actual treatments received. Subjects will not be excluded from this population as a result of changes to the background regimen. The safety population will be the primary population for safety analyses. All safety analyses will be produced using the safety population.

Section 8.3.3 - Treatment Comparisons

Original text:

Primary Comparisons of Interest

The primary efficacy analysis will be performed at Week 24 based on the proportion of subjects in the ITT-E population with plasma HIV-1 RNA <50 c/mL using MSDF algorithm. The primary comparison of interest will be performed using a Bayesian probability model. The probability of (Response rate for LA arm ≤ Response rate for Oral arm -10%) will be calculated.

Other Comparisons of Interest

The secondary efficacy analysis will be performed to evaluate the impact of the duration of suppression, based on 16 or 24 weeks of 30 mg GSK744 once daily in combination with ABC/3TC on the ability of a regimen of 400 mg IM of GSK744 LA plus 600 mg IM of TMC278 LA every 4 weeks to maintain virologic suppression through Week 96. Measures of safety and tolerability will be assessed as detailed in the RAP

Revised text:

Primary Comparisons of Interest

The primary efficacy analysis will be performed at Week 32 based on the proportion of subjects in the ITT-ME population with plasma HIV-1 RNA <50 c/mL using MSDF algorithm. The primary comparison of interest will be the response rate of each IM dosing arm to the oral control arm performed using a Bayesian probability model. The probability of (Response rate for IM arm ≤Response rate for Oral arm -10%) will be calculated.

Other Comparisons of Interest

The probability of Q8W comparable to Q4W will be provided using the Bayesian probability model.

Section 8.3.4 - Interim and Final Analysis

Original text:

The ITT-E population will be primary efficacy population and the safety population will be the primary safety population for all analyses. All available data will be included in all interim analyses, including data beyond the designated time point except for the Day 1 analysis, if preformed, will only include data from the Induction Period.

At the first interim analysis the IDMC will evaluate the efficacy, safety and tolerability of GSK744 to determine if the GSK744 regimen is suboptimal such that it should be discontinued before all subjects transition into the Maintenance Period of the study. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

This interim analysis schedule does not require an adjustment for multiplicity since there is no possibility of a false positive finding at any of the interim analyses conducted before Week 24, and since the Week 48 and 96 analyses will be used to further characterise the long-term safety and efficacy profile of GSK744. As no hypothesis is being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity will be performed.

Futility interim monitoring

Plasma HIV-1 RNA data will be monitored closely as subjects enter the Maintenance Period in order to prevent subjects from continuing on a regimen if existing data indicates that they are at unacceptable risk of inadequate maintenance of virologic suppression.

The number of protocol defined virologic failures during the Maintenance Period will be monitored in all subjects that had at least 4 weeks of the maintenance dose regimen on LA (Week 4). If the number of failures meets or exceeds the thresholds specified in the table below (Table 6) this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review and possible discontinuation of that treatment arm. If an inadequate response is seen in the shorter induction length arm and it is determined that that arm should be discontinued, then subjects on that treatment arm still in the Induction Period can be switched to the longer induction length.

Table 6 Number of protocol-defined virologic failures on Maintenance Period that constitute strong evidence of inadequate virologic response

Number of subjects that had at least four weeks of maintenance dose on LA	Number of protocol-defined virologic failures after maintenance dose on LA
3-21	>=3
22-32	>=4
33-43	>=5
44-54	>=6
55-65	>=7
66-75	>=8
76-86	>=9
87-97	>=10
98-100	>=11

The thresholds described in this table are derived on the basis of the ratio of the likelihoods for the null hypothesis (H_0) that there is a subgroup of subjects with inadequate maintenance of virologic suppression and the alternative hypothesis (H_1) that the only failures in the study are due to poor compliance. For this analysis, H_0 translates to a protocol defined virologic failure rate of 20% or higher (as defined in Section 4.6) and H_1 translates to an expected 3% rate of protocol defined virologic failures. Further details on this method are contained in Section 11.5. Each threshold represents strong evidence in favour of H_0 over H_1 [Royall, 1997].

The scenarios described above are not exhaustive – it is possible that the overall failure rate does not meet the threshold but that a subgroup of subjects (e.g. with a given combination of mutations or fold resistance to GSK744 above an as yet unknown threshold) are consistently failing. GSK will monitor virologic response by Baseline genotype and may halt one or more treatment arms if at any time subjects are deemed to be at an unacceptable risk of an inadequate response on the basis of such monitoring, although the high number of possible genotypic subgroups precludes pre-specification of precise thresholds for such action.

IDMC Interim Analyses

The purpose of these analyses is for the Independent Data Monitoring Committee (IDMC) to evaluate the efficacy, safety and tolerability of GSK744 at early time points in

the study. The IDMC will review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter, with IDMC agreement.

As subjects enter the Maintenance Period of the study, the protocol defined virologic failure rate will be continually monitored. If the number of failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

Day 1 Interim Analysis

A Day 1 interim analysis may be conducted to support regulatory submissions and/or scientific conference presentations once the last randomized subject has completed the Day 1 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to evaluate efficacy, safety and tolerability of GSK744 30 mg once daily plus ABC/3TC once daily in the Induction Period. Only data from the Induction Period would be summarized in this analysis.

Week 24 Primary Analysis

The Week 24 primary analysis will be conducted once the last randomized subject has completed the Week 24 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of the long-acting regimen of GSK744 LA + TMC278 LA.

Week 48 Interim Analysis

The Week 48 interim analysis will be conducted once the last randomized subject has completed the Week 48 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the safety, tolerability and durability of antiviral response of the long- acting regimen of GSK744 LA + TMC278 LA.

Week 96 Final Analysis

The Week 96 final analysis will be conducted once the last randomized subject has completed the Week 96 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to fully characterise the long term safety and efficacy profile of the long-acting regimen of GSK744 LA + TMC278 LA.

Additional analyses may be performed as needed. The primary and interim analyses may be used to support regulatory submissions and/or scientific conference presentations

Revised text:

The ITT-ME population will be primary efficacy population and the safety population will be the primary safety population for all analyses. All available data will be included in all interim analyses, including data beyond the designated time point except for the Day 1 analysis, if preformed, will only include data from the Induction Period.

At the first interim analysis the IDMC will evaluate the efficacy, safety and tolerability of GSK744 to determine if the GSK744 regimen is suboptimal such that it should be discontinued before all subjects transition into the Maintenance Period of the study. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

This interim analysis schedule does not require an adjustment for multiplicity since there is no possibility of a false positive finding at any of the interim analyses conducted before Week 32, and since the Week 48 and 96 analyses will be used to further characterise the long-term safety and efficacy profile of GSK744. As no hypothesis is being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity will be performed.

IDMC Interim Analyses

The purpose of these analyses is for the Independent Data Monitoring Committee (IDMC) to evaluate the efficacy, safety and tolerability of GSK744 at early time points in the study. The IDMC will review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter, with IDMC agreement.

All the IDMC reviews will be produced by a Statistics and Data Analysis Centre (SDAC).

Futility Interim Monitoring

Continuous monitoring of the number of protocol defined virologic failures during the Maintenance Period and a futility interim analysis when 50% subjects have completed Week 24 is planned.

Continuous Monitoring

Plasma HIV-1 RNA data will be monitored closely as subjects enter the Maintenance Period in order to prevent subjects from continuing on a regimen if existing data indicates that they are at unacceptable risk of inadequate maintenance of virologic suppression. The number of protocol defined virologic failures during the Maintenance Period will be monitored in all subjects that have at least 4 weeks of either of the Maintenance Period IM dosing regimens (Week 4). If the number of failures meets or exceeds the thresholds specified in the table below (Table 6) this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review and possible discontinuation of that treatment arm. If an inadequate response is seen in any arm and it is determined by IDMC that that arm should be discontinued, then subjects on that treatment arm can be switched to the remaining IM arm.

Table 6 Number of protocol-defined virologic failures on Maintenance Period that constitute strong evidence of inadequate virologic response

Number of subjects that had at least four weeks of maintenance dose on IM	Number of protocol-defined virologic failures after maintenance dose on IM
3-21	>=3
22-32	>=4
33-43	>=5
44-54	>=6
55-65	>=7
66-75	>=8
76-86	>=9
87-97	>=10
98-100	>=11

The thresholds described in this table are derived on the basis of the ratio of the likelihoods for the null hypothesis (H_0) that there is a subgroup of subjects with inadequate maintenance of virologic suppression and the alternative hypothesis (H_1) that the only failures in the study are due to poor compliance. For this analysis, H_0 translates to a protocol defined virologic failure rate of 20% or higher (as defined in Section 4.6) and H_1 translates to an expected 3% rate of protocol defined virologic failures. For the first IDMC review, if the true rate of virologic failure is 20% as specified in H_0, the probability to detect the inadequate virologic suppression is greater than 70%. If the true rate of virologic failure is 3%, the probability to see number of virology failure exceed the threshold is less than<1%. Further details on this method are contained in the IDMC charter. Each threshold represents strong evidence in favour of H_0 over H_1 [Royall, 1997].

The scenarios described above are not exhaustive – it is possible that the overall failure rate does not meet the threshold but that a subgroup of subjects (e.g. with a given combination of mutations or fold resistance to GSK1265744 above an as yet unknown threshold) are consistently failing. GSK will monitor virologic response by Baseline genotype and may halt one or more treatment arms if at any time subjects are deemed to be at an unacceptable risk of an inadequate response on the basis of such monitoring, although the high number of possible genotypic subgroups precludes pre-specification of precise thresholds for such action.

Futility Analysis after 50% of subjects complete Week 24

An interim analysis for the purpose of review by the IDMC will be performed after approximately 50% of subjects complete Week 24. A futility rule based on Bayesian posterior probability approach will be applied to assess the probability that the IM treatment arm demonstrates the comparability with the oral control arm given the partial data set. Posterior probabilities of success (Prob ($p_{IM} > p_{oral} - 0.1$ | data)) are provided in Table 7 for a subset of possible outcomes that could occur at the interim. Those outcomes associated with a posterior probability of success <40% may trigger a comprehensive IDMC data review and possible discontinuation of that treatment arm, although all data will be taken into consideration for making this decision.

Table 7 Posterior Probability of Success[a] at the Interim Analysis Under Various Scenarios

		# Successes in IM arm (out of 45)							
		35 (78%)	36 (80%)	37 (82%)	38 (84%)	39 (87%)	40 (89%)	41 (91%)	42 (93%)
# Successes in Oral arm (out of 23)	18(78%)	0.564	0.678	0.753	0.850	0.913	0.955	0.979	0.993
	19(83%)	0.454	0.558	0.679	0.782	0.859	0.931	0.966	0.986
	20(87%)	0.346	0.465	0.574	0.694	0.805	0.890	0.942	0.974
	21(91%)	0.244	0.348	0.455	0.584	0.706	0.829	0.907	0.961
	22(96%)	0.146	0.231	0.335	0.461	0.604	0.736	0.845	0.926
	23(100%)	0.081	0.135	0.218	0.324	0.473	0.612	0.755	0.874

c. Posterior probability of success is defined as (prob($p_{IM} > p_{oral} - 0.1$ | data)) with informative prior Beta (23,2) for oral arm and non-informative prior Beta (1,1) for IM arm.

d. Highlighted cells represent outcomes with posterior probability <0.4 that may trigger a comprehensive IDMC data review.

The proposed the futility analysis has 91% chance to stop the study at the interim analysis if the true response rates are 92% and 72% for the oral arm and IM arm, respectively. The power to stop the study is 46% if the true response rates are 92% and 82% for the oral arm and IM arm, respectively. The chance of stopping the study by error is 2% if the true response rates are 92% for both the oral arm and IM arm.

Day 1 Interim Analysis

A Day 1 interim analysis may be conducted to support regulatory submissions and/or scientific conference presentations once the last randomized subject has completed the Day 1 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to evaluate efficacy, safety and tolerability of GSK744 30 mg once daily plus ABC/3TC once daily in the Induction Period. Only data from the Induction Period would be summarized in this analysis.

Week 32 Primary Analysis

The Week 32 primary analysis will be conducted once the last randomized subject has completed the Week 32 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of both IM dosing regimens of GSK744 LA + TMC278 LA and to select a regimen for further development should both IM dosing regimens be comparable to the oral control arm.

Week 48 Interim Analysis

The Week 48 interim analysis will be conducted once the last randomized subject has completed the Week 48 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the safety, tolerability and durability of antiviral response of both IM dosing regimens of GSK744 LA + TMC278 LA and to confirm the selected regimen for further development should both IM dosing regimens be comparable to the oral control arm.

Week 96 Final Analysis

The Week 96 final analysis will be conducted once the last randomized subject has completed the Week 96 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to fully characterise the long term safety and efficacy profile of both IM dosing regimens of GSK744 LA + TMC278 LA.

Follow-up analyses after the Week 96 analysis of data collected after subjects have switched to the chosen dose of GSK744 LA may be conducted to more fully characterize the long-term safety and efficacy profile of GSK744 LA.

Section 8.3.5 - Key Elements of Analysis Plan

Revised to (changes struck through and underlined).

Efficacy Analyses

All efficacy analyses, except as stated otherwise, will be based on the ITT-ME population.

The primary efficacy analysis will be based on the MSDF approach mentioned in Section 8.3.2. For the MSDF analysis, any switches in background ART after HIV-1 RNA has been collected ~~will~~may be considered as failures even if the switch was done to manage intolerance issues. Plasma HIV-1 RNA will be $\log_{10}$-transformed prior to statistical analyses. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window ~~will be listed and~~ will be included in the derivation of the time to loss of virologic response, but summary tables using OC datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any deviations from the planned analyses described in this protocol or the RAP will be detailed in the clinical study report (CSR).

And:

Original text:

For the analysis of GSK744 LA+TMC278 LA arm (LA arm) response rate relative to GSK744 + ABC/3TC (oral arm), let:

X_{LA} = number of responder in LA arm, and

X_{oral} = number of responder in oral arm

The binomial distribution is the assumed likelihood of the eRVR data, as follows:

$X_{LA} \sim$ Binomial (100, p_{LA})

$X_{oral} \sim$ Binomial (50, p_{oral})

Since the true response rate is unknown, prior distributions are placed on these parameters of interest to reflect current beliefs and balanced with acceptable decision criteria performance. Conjugate beta densities are assumed. The information pertaining to the oral arm response rate is well understood and the prior that was chosen reflects the belief that the response rate is between 88% and 99% with 94% certainty. There is very few information about the response rate for LA arm, therefore, a non-informative prior assumed.

$P_{LA} \sim$ Beta (1, 1)

$P_{oral} \sim$ Beta (44, 2.6)

The posterior probability that the response rate for LA arm demonstrates the comparability of oral arm is as follows:

$p_1 = P (P_{LA} > p_{oral} - 0.1 \mid \text{data})$

A posterior probability of at least 90% (i.e., $p_1 > 0.90$) corresponds to "substantial evidence of positive outcome" and is chosen as the weight of evidence threshold.

Sensitivity analyses may be performed to assess the impact of the choice of informative prior for oral arm response rate though the analysis described above will remain primary for indication of efficacy decision-making purposes. As an alternative to the informative prior, a Beta (1, 1) prior distribution for oral arm may be considered. Full details of the planned Bayesian analyses will be provided in the RAP.

The proportion of subjects with plasma HIV-1 RNA <50 c/mL as determined by the MSDF algorithm will be provided by treatment group and induction length over the entire time on study by visit for the ITT-E population and the ITT-ME population.

In addition, an OC analysis will be performed for supportive purposes.

Revised text:

For the analysis of GSK744 LA+TMC278 LA arms (IM arms) response rate relative to GSK744 + ABC/3TC (oral arm), let:

X_{LA} = number of responder in IM arm, and

X_{oral} = number of responder in oral arm

The binomial distribution is the assumed likelihood of the response data, as follows:

$X_{LA} \sim$ Binomial (90, p_{IM})

$X_{oral} \sim$ Binomial (45, p_{oral})

Since the true response rate is unknown, prior distributions are placed on these parameters of interest to reflect current beliefs and balanced with acceptable decision criteria performance. Conjugate beta densities are assumed. The information pertaining to the oral arm response rate is well understood and the prior that was chosen reflects the belief that the response rate is between 78% and 99% with 95% certainty. There is very few information about the response rate for IM arm, therefore, a non-informative prior assumed.

$P_{LA} \sim$ Beta (1, 1)

$P_{oral} \sim$ Beta (23, 2)

The posterior probability that the response rate for IM arm demonstrates the comparability of oral arm is as follows:

$p_1 = P (P_{IM} > p_{oral} - 0.1 \mid data)$

A posterior probability of at least 90% (i.e., $p_1 > 0.90$) corresponds to "substantial evidence of positive outcome" and is chosen as the weight of evidence threshold.

Sensitivity analyses may be performed to assess the impact of the choice of informative prior for oral arm response rate though the analysis described above will remain primary for indication of efficacy decision-making purposes. As an alternative to the informative prior, a Beta (1, 1) prior distribution for oral arm may be considered. Full details of the planned Bayesian analyses will be provided in the RAP.

The proportion of subjects with plasma HIV-1 RNA <50 c/mL as determined by the MSDF algorithm will be provided by treatment group over the entire time on study by visit for the ITT-ME population and the ITT-E population.

In addition, an OC analysis will be performed for supportive purposes.

For the probability of comparability between two IM arms, a non-informative prior of Beta (1, 1) will be used for both IM treatment arms.

Section 8.3.5.2 - Safety Analyses

Added:

Framingham Risk assessment will be calculated as detailed in the RAP and will be summarized by treatment arm.

Section 11.2 – Appendix 2

Removed the Child-Pugh Appendix.

Section 11.4 – Appendix 5

Removed the Statistical Method for Plasma HIV-1 RNA Monitoring. This is now in the RAP.

Section 11 – New Appendix

With the removal and addition of Appendices, this Appendix is now number 4.

Added the following information regarding liver stopping criteria and restarting / rechallenging study drug:

VSLC GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

3. **Drug rechallenge** may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternative medicine available (Table 8, Figure 7)
4. In Phase III, **drug restart** may be considered for liver events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not associated with HLA marker of liver injury, when liver chemistries improve to within 1.5xbaseline and ALT<3xULN) (Table 9, Figure 8).

Background: Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered in one month of initial injury [Andrade , 2009]. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

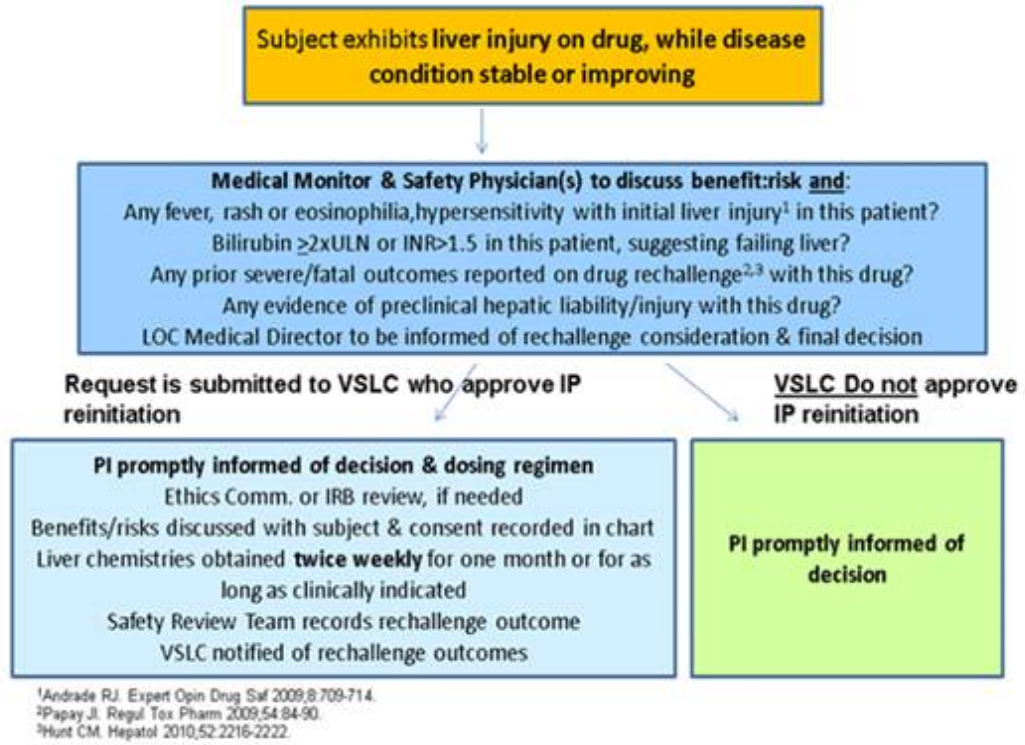
- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade 2009]
- jaundice or bilirubin≥2xULN with initial liver injury

- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay , 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

VSLC Decision Process for Drug Rechallenge Approval or Disapproval (See Figure 7)

- Principal Investigator (PI) requests consideration of drug rechallenge for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment
- By definition treatment naïve subjects will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician to review the subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 8).
- The Medical Monitor and GCSP Physician are accountable to review and agree on:
  - compelling benefit of the investigational product (IP) for this subject and no alternative therapy
  - must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history
  - Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
    - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin≥2xULN (or direct bilirubin >35% of total, if available)
    - subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5
    - SAE or fatality has earlier been observed with IP rechallenge
    - IP associated with known preclinical hepatic liability/ injury
- Relevant physicians must review and agree on request for drug rechallenge:
  - Safety Team Leader, VP, or Senior Safety Physician (GSK)
  - Medicines Development Leader and Project Physician Leader (GSK)
  - Request is taken to full VSLC for final decision

Figure 7 VSLC process for drug rechallenge approval or disapproval



The local operating company (LOC) ViiV medical director (and GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.

Table 8 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin≥2xULN (direct bilirubin >35% of total)		
○ Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5		
○ SAE or fatality has earlier been observed with IP rechallenge **If yes, please provide brief explanation**:		
○ IP associated with known preclinical hepatic liability/ injury		
○ Source data defining the patients current resistance profile		
○ Previous drug history		

Drug Restart

Phase II "drug restart" can be approved by the VSLC for transient, defined non-drug-induced liver injury if no evidence of:

- immunoallergic injury /HLA association with injury
- DILI
- alcoholic hepatitis

Study drug held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 8):

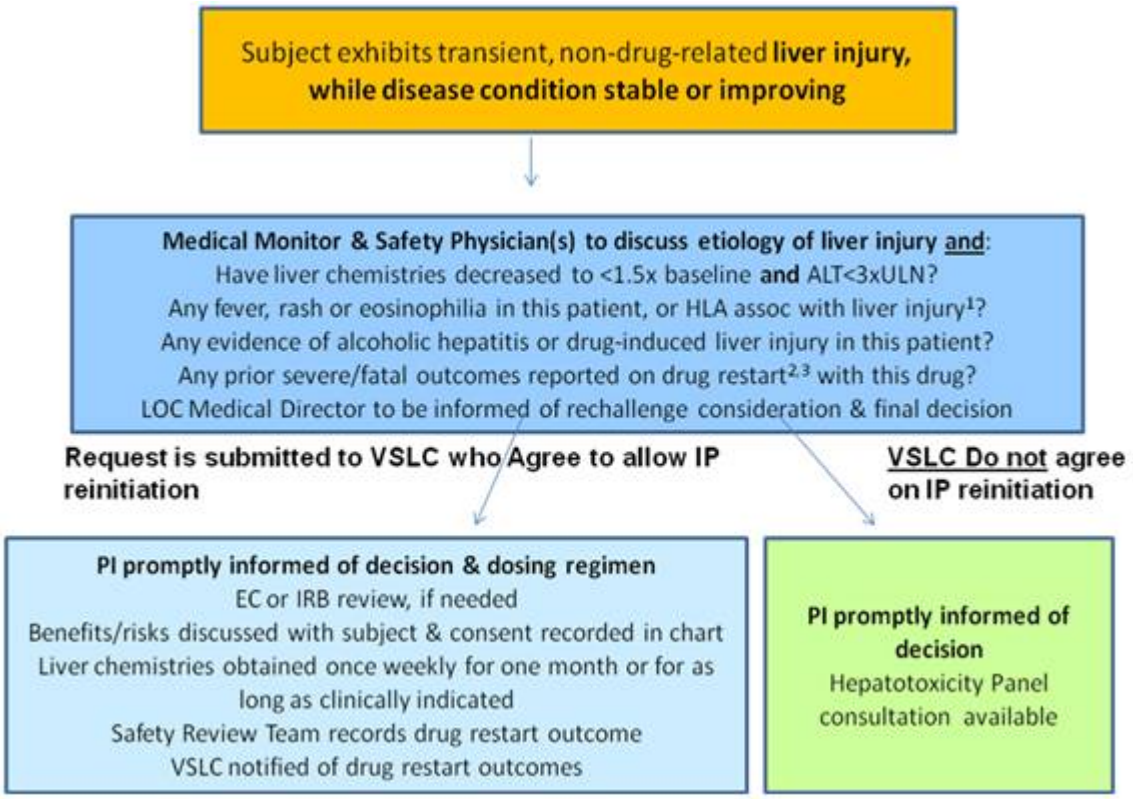
- PI requests consideration of drug re-initiation for a subject stable or improving on IP, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- GSK Medical Monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 9).
  - must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history.
- The LOC ViiV medical director (and GSK where applicable) should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.

Table 9 Checklist for Phase II drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chemistry ≤ 1.5x baseline & ALT<3xULN

	Yes	No
Is subject stable or improving on the investigational product (IP)?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the patients current resistance profile		
Previous drug history		

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader (GSK).
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this subject must be recorded by GCSP Physician and sent to the VSLC Secretary.
- VSLC must approve drug re-initiation and dosing regimen

Figure 8 VSLC process for drug restart approval or disapproval



1. Andrade 2009; 2. Papay , 2009; 3. Hunt, 2010

Medical monitor, GCSP Physician and PI actions for Restart or Rechallenge following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.

- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC
- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug rechallenge (or restart) must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy (ViiV) and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain IRB/EC approval of drug rechallenge or restart, as required.
- If drug re-initiation VSLC-approved, the patient must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
  - Targeted drug rechallenge or drug restart consent form must be used.
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed twice weekly for 'rechallenge' cases and once weekly for 'restart' cases for one month or for as long as clinically indicated following drug re-initiation. If subject exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.

VSLC and the IRB/EC must be informed of the patient's outcome following drug rechallenge or restart.

Rechallenge/restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

REFERENCES:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

Amendment 3

Amendment 3 applies to all countries and all sites. Primary modifications are as follows: Epzicom / Kivexa added as Investigational Product beginning at Day 1 of the Maintenance Period; clarification that alternative background therapy (if positive for HLA-B*5701) is not counted as the protocol permitted switch for NRTI; clarification regarding provision of alternative NRTI therapy; clarification that Exclusion for treatment of hepatitis C infection is exclusionary at any time during the study; removed example of effective barrier method from Inclusion criteria; change in visit window for subjects on the oral dosing arm; excursion temperatures added for Epzicom / Kivexa and Edurant; text added for Epzicom / Kivexa overdose; simplified text for results from primary analysis; deleted option for subject informed consent by legal representative; deleted duplicate text for "lack of efficacy"; added RPV pre-dose pharmacokinetic (PK) sample at Day 1 to PK table; updated PK information for LAI116482 subject with integrase and NNRTI resistance; updated operating characteristic figure to include legend for 94% response; Time and Events Table clarifications: 1) added the collection of HIV risk factors at Screening (or a later visit); 2) added collection of plasma for storage at time of confirmation of virologic failure; 3) subjects should have PK sample drawn **prior** to dosing; 4) safety assessments should be conducted every 16 weeks if every 8 weeks is chosen for the extension schedule; 5) simplified ECG assessments for oral Maintenance arm; 6) created new row in Table to separate CD4+ and CD8+ cell counts; corrected typographical errors, updated and/or corrected list of abbreviations, Trademarks, and references.

List of Abbreviations – Updated to remove abbreviations not used within the protocol, added abbreviation for FTC.

Trademark List – Updated to remove Trademarks not referenced within the protocol.

Protocol Summary and Section 1.2.: List of Study Terms – updated to include Epzicom / Kivexa as IP starting at Day 1 – based on Regulatory feedback from France.

Original Text:

- IP = Investigational product; both formulations of GSK1265744 and TMC278.

Revised Text:

- IP = Investigational product; both formulations of GSK1265744 and TMC278. <u>Epizcom / Kivexa will also be considered IP beginning at Day 1 of the Maintenance Period.</u>

Protocol Summary: Notable Inclusion Criteria –corrected typo for "≥"

Original Text:

- Male or female subjects at least 18 years old that are HIV-1 positive (HIV-1 RNA > 1000 copies/millilitre [c/mL])

Revised Text:

- Male or female subjects at least 18 years old that are HIV-1 positive (HIV-1 RNA ≥ 1000 copies/millilitre [c/mL])

Protocol Summary: Notable Exclusion Criteria – clarification that treatment for hepatitis C infection is not permitted at any time during the study:

Original Text:

- History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (HBsAg positive). Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy ~~during the randomized portion of the study~~ must be excluded.

Revised Text:

- History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (HBsAg positive). Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy must be excluded.

Protocol Summary: Study Design: Maintenance Period AND Section 3.2.4. Maintenance Period – clarification of timing of dosing windows:

Original Text:

A (+ or -) 7 day window is allowable for IM dosing but not preferred. ~~Oral dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Baseline visit).~~

Revised Text:

A (+ or -) 7 day window, <u>from the projected visit date,</u> is allowable for IM dosing but not preferred.

<u>Visits for subjects on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit.</u>

Protocol Summary: Study Design: Maintenance Period: Entering from the GSK744 + ABC/3TC Arm – Typo Correction:

Original Text:

At Week 104, subjects will receive their last dose of GSK744 + ABC/3TC + RPV in the clinic and will begin IM dosing with the selected ~~the~~ IM regimen.

Revised Text:

At Week 104, subjects will receive their last dose of GSK744 + ABC/3TC + RPV in the clinic and will begin IM dosing with the selected IM regimen.

Protocol Summary: Study Design: Long-term Follow-Up Period IM Regimens AND Section 3.2.6. Long-term Follow-Up Period – IM Regimens only - clarification on provision of alternative NRTI therapy:

Original Text:

In order to assure that subjects have access to HAART during the Long-Term Follow-Up Period, ~~the Sponsor will reimburse sites for HAART prescribed~~ during this period.

Revised Text:

In order to assure that subjects have access to HAART during the Long-Term Follow-Up Period, GSK may supply HAART regionally or reimbursement will be provided during this period.

Protocol Summary: Permitted Treatment Substitutions AND Section 5.6. Protocol Permitted Substitutions AND Setion 6.7. Time and Events Table – Long-Term Follow-Up – footnote e – clarification regarding provision of alternative NRTI therapy.

Original Text:

This regimen ~~will not be provided by GSK, but the Sponsor will reimburse sites for this cost.~~

Revised Text:

This regimen may be supplied regionally by GSK or reimbursement will be provided.

Protocol Summary: Primary Analysis – clarification of how analysis will be used.

Original Text:

The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of both IM dosing regimens of GSK744 LA + TMC278 LA and to select a regimen for further development ~~should both IM dosing regimens be comparable to the oral control arm~~.

Revised Text:

The results of this analysis will be used to characterize safety, tolerability and durability of antiviral response of both IM dosing regimens of GSK744 LA + TMC278 LA and to select a regimen for further development.

Section 1.4. GSK1265744 – Long Acting Injectable (GSK744 LA) – correction of typo

Original Text:

GSK744 LA ~~(~~has been generally well-tolerated as either an IM or SC dose. Intramuscular injection site reactions (ISRs) have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date.

Revised Text:

GSK744 LA has been generally well-tolerated as either an IM or SC dose. Intramuscular injection site reactions (ISRs) have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date.

Section 1.5. TMC278 – Oral (RPV) – clarification provided regarding Week 48 analysis, reference updated.

Original Text:

The Week 48 efficacy outcome for the pooled data from TMC278-C209 and TMC278-C215 (N=136~~0~~) showed that the proportion of subjects with HIV-1 RNA < 50 c/mL was 83% for RPV based regimen compared to 80% for the EFV based regimen. The overall virologic failure rate was 13% for the RPV compared to 9% for EFV. The proportion of patients who discontinued study due to an adverse event or death was 2% for RPV and 7% for EFV [~~Edurant Product Information, 2013~~].

Revised Text:

The Week 48 efficacy outcome for the pooled data from TMC278-C209 and TMC278-C215 (N=136<u>8</u>) showed that the proportion of subjects with HIV-1 RNA < 50 c/mL was 83% for RPV based regimen compared to 80% for the EFV based regimen <u>(Snapshot algorithm)</u>. The overall virologic failure rate was 13% for the RPV compared to 9% for EFV. The proportion of patients who discontinued study due to an adverse event or death was 2% for RPV and 7% for EFV [Cohen<u>, 2012</u>].

Section 1.7. Study LAI116482 – updated PK information for Subject PPD

Original Text:

~~Week 48 PK for this subject is pending.~~

Revised Text:

The Week 40 and Week 48 PK for this subject was consistent with Maintenance Phase Individual Average pre-dose values determined prior to the reported dates of calorie restriction.

Section 1.10.1.2. TMC278, Section 3.3. Discussion of Design, Section 5.1.2. TMC278 – Tablet (Rilpivirine, RPV) - Updated Reference

Original Text:

[Edurant Product Information, 2013].

Revised Text:

[Edurant Product Information, 2014].

Section 3.2.1. Screening Period – clarification of background switch and provision of alternative NRTI therapy.

Original Text:

Subjects who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on a dual-NRTI backbone that does not contain abacavir; ~~this would comprise the single allowed NRTI switch for this subject~~. The ~~cost of the~~ selected dual-NRTI backbone will be reimbursed by the Sponsor.

Revised Text:

Subjects who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on a dual-NRTI backbone that does not contain abacavir. The selected dual-NRTI backbone may be supplied regionally by GSK or reimbursement will be provided.

Section 4.2. Inclusion Criteria – Criteria 2 – removed example of effective barrier method.

Original Text:

ALL subjects participating in the study must be counseled on safer sexual practices including the use of effective barrier methods ~~(e.g. male condom/spermicide)~~ to minimize risk of HIV transmission.

Revised Text:

ALL subjects participating in the study must be counseled on safer sexual practices including the use of effective barrier methods to minimize risk of HIV transmission.

Section 4.3. Exclusion Criteria – Criteria 7 – clarification that hepatitis C treatment would be exclusionary at any time during the study.

Original Text:

7. History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (HBsAg positive). Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy ~~during the randomized portion of the study~~ must be excluded.

Revised Text:

7. History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic hepatitis B virus (HBV) infection (HBsAg positive). Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; subjects who are anticipated to require such therapy must be excluded.

Section 4.6.2.2. Confirmed Virologic Sample – added plasma sample collection from the confirmation visit.

New Text Added:

A plasma sample from the confirmation visit will be obtained for storage. This sample may be used for possible future analyses, e.g. for genotypic and phenotypic analyses of subjects who experience virologic failure.

Section 5.1. Investigational Product and Other Study Treatment – Changed Epzicom / Kivexa to IP at Day 1 and clarification regarding other background therapy supplies.

Original Text:

In this study, investigational product (IP) refers to GSK744, GSK744 LA, RPV and TMC278 LA. These will be supplied by GlaxoSmithKline and Janssen Pharmaceuticals, respectively.

Other antiretrovirals administered in the study as dual background NRTIs are not considered IP. ~~However,~~ these ~~will be~~ supplied by GSK or, ~~in some cases,~~ reimbursement will be provided.

Revised Text:

In this study, investigational product (IP) refers to GSK744, GSK744 LA, RPV and TMC278 LA. These will be supplied by GlaxoSmithKline and Janssen Pharmaceuticals,

respectively. Epzicom / Kivexa will also be considered IP from Day 1 of the Maintenance Period and will be provided by GSK.

Other antiretrovirals administered in the study as dual background NRTIs (e.g. for subjects who are HLA-B*5701 positive or switch due to toxicity) are not considered IP. These may be supplied regionally by GSK or reimbursement will be provided.

Section 5.1.2. TMC278 – Tablet (Rilpivirine, RPV) – Added Excurion temperatures.

Original Text:

RPV tablets are to be stored at 25°C and protected from light.

Revised Text:

RPV tablets are to be stored at 25°C (excursions permitted to 15°-30°C [59°-86°F]) and protected from light.

Section 5.1.3. Background NRTIs – Section title changed, Reference Information clarification, excursion temperatures added.

Original Text:

5.1.3. ~~Background NRTIs~~

ABC/3TC [Epzicom~~/Kivexa~~ Product Information, 2012] is manufactured by GlaxoSmithKline and is supplied as the ABC/3TC fixed dose combination (FDC) oral tablet, which contains 600 mg of ABC (as abacavir sulfate) and 300 mg of 3TC. The tablets are orange, film-coated, modified capsule-shaped and debossed with GS FC2 on one side with no markings on the reverse side. ABC/3TC is packaged in bottles of 30 tablets. ABC/3TC will be supplied by GSK as commercial product. ABC/3TC tablets are to be stored at 25°C.

Revised Text:

5.1.3. Epzicom / Kivexa

ABC/3TC [Epzicom Product Information, 2012] is manufactured by GlaxoSmithKline and is supplied as the ABC/3TC fixed dose combination (FDC) oral tablet, which contains 600 mg of ABC (as abacavir sulfate) and 300 mg of 3TC. The tablets are orange, film-coated, modified capsule-shaped and debossed with GS FC2 on one side with no markings on the reverse side. ABC/3TC is packaged in bottles of 30 tablets. ABC/3TC will be supplied by GSK as commercial product. ABC/3TC tablets are to be stored at 25°C (excursions permitted to 15°-30°C [59°-86°F]).

Section 5.7.1 Oral Dosing – Clarification of Visit Window.

Original Text:

~~**Oral dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Baseline visit).**~~

Revised Text:

Visits for subjects on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit.

Section 5.7.2. IM Dosing AND Section 6.10.6.1. – dosing window clarification.

Original Text:

An additional (+ or -) 7 day window is allowable for IM dosing but not preferred.

Revised Text:

An additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred.

Section 5.8. Discontinuation of Study Treatment – deleted name of IP since different between Induction and Maintenance.

Original Text:

Subjects unable to manage drug toxicity or tolerate investigational product ~~(IP, either formulations of GSK1265744 or TMC278)~~ must have IP discontinued.

Revised Text:

Subjects unable to manage drug toxicity or tolerate investigational product must have IP discontinued.

Section 5.9.2. Prohibited Medications and Non-Drug Therapies – clarifications.

Original Text:

Chronic use of oral glucocortic~~oster~~oids must be avoided; however, short treatment courses (e.g., 10 days or less) and topical, inhaled or intranasal use of glucocortic~~oster~~oids will be allowed.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen, please consult the local prescribing information.

Revised Text:

Chronic use of oral glucocorticoids must be avoided; however, short treatment courses (e.g., 10 days or less) and topical, inhaled or intranasal use of glucocorticoids will be allowed.

Hepatitis C infection treatment will not be permitted during the study.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen (e.g. Epzicom / Kivexa), please consult the local prescribing information.

Section 5.10.1. Long-Term Follow-Up Period – clarification regarding provision of alternative NRTI therapy.

Original Text:

The Sponsor will not provide this regimen but will reimburse sites for cost.

Revised Text:

GSK may supply HAART regionally or reimbursement will be provided.

Section 5.11. Treatment of Study Treatment Overdose – overdose information provided for Epzicom / Kivexa.

New Text Added: For subjects receiving Epzicom / Kivexa, any tablet intake exceeding the protocol defined daily number of tablets (one tablet daily) will be considered an overdose.

Section 6.1. Time and Events Table – Induction Period, Section 6.2. Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q8W), AND Section 6.3. Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q4W) – clarification provided.

Split CD8+ cell count into new row in table.

Section 6.1 Time and Events Table – Induction Period – Footnote a – clarification for subjects who begin the Induction Period (no longer randomized at Induction).

> **Footnote a:** Original Text:
>
> Subjects may ~~be randomized and~~ begin the Induction Period as soon as all Screening assessments are complete.
>
> Revised Text:
>
> Subjects may begin the Induction Period as soon as all Screening assessments are complete.

Demography: Moved collection from Week (-20) to Screening Period.

Footnote f: Addition of HIV Risk Factors and clarification of when data is reported in InForm

Original Text:

f. Collect full routine medical history plus: cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders.

Revised Text:

f. Collect full routine medical history plus <u>(report at Baseline visit): HIV risk factors (may be collected at a later study visit),</u> cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal and neurologic disorders.

HIV-1 RNA and sample for storage: "and genotype" added for clarification at Screening visit.

Section 6.2. Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q8W) – clarification.

PK Sample for Storage – changed to "X" at Withdrawal Visit.

Section 6.2. Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q8W) AND Section 6.3. Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q4W) – clarification provided.

Footnotes l and m:

Original Text:

l) Subjects should take GSK744+ABC/3TC+RPV on Day 1 in the clinic ~~prior to~~ PK sampling and injections should be administered within 2 hours of this where possible.

m) .....**IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred.....**

Revised Text:

l) Subjects should take GSK744+ABC/3TC+RPV on Day 1 in the clinic <u>after</u> PK sampling and injections should be administered within 2 hours of this where possible.

m) .....**IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, <u>from date of projected visit,</u> is allowable for IM dosing but not preferred.....**

Section 6.4. Time and Events Table – Maintenance Period for Oral Regimen (GSK744 + ABC/3TC) – simplified ECG schedule to be consistent with IM regimens. Removed ECGs at Week 56, Week 72, and Week 88.

Section 6.5. Time and Events Table – Extension Period if Q8W is Selected – clarification for timings in footnote c.

Original Text:

c. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 1~~84~~, Week 216 will be conducted just like Week ~~192~~ and Week 224 will be conducted just like Week ~~200~~.

Revised Text:

c. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 192, Week 216 will be conducted just like Week 200 and Week 224 will be conducted just like Week 192.

Section 6.5. Time and Events Table – Extension Period if Q8W is Selected AND Section 6.6. Time and Events Table – Extension Period if Q4W is Selected – clarifications provided:

PK Sample for Storage: Changed to "X" at Withdrawal Visit.

Footnote l (Section 6.5.) and Footnote k (Section 6.6.) – Clarification regarding dosing window:

Original Text:

.....IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window is allowable for IM dosing but not preferred.......

Revised Text:

.....IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, <u>from date of projected visit</u>, is allowable for IM dosing but not preferred.......

Section 6.7. Time and Events Table – Long-Term Follow Up Period – clarification provided.

PK Sample for Storage: Changed to "S" at all visits during this period.

Section 6.8. Critical Screening and Baseline Assessments – clarification provided regarding legal representative – per French Regulatory request.

Original Text:

Written informed consent must be obtained from each potentially eligible subject ~~(or his/her legal representative)~~ by study site personnel **prior** to the initiation of any Screening procedures as outlined in this protocol.

Revised Text:

Written informed consent must be obtained from each potentially eligible subject by study site personnel **prior** to the initiation of any Screening procedures as outlined in this protocol.

Section 6.8.2. Baseline – clarification provided.

Original Text:

In addition to a full routine medical history ~~at Baseline~~, more detailed information will be collected for some disease processes such as:

Revised Text:

In addition to a full routine medical history, more detailed information will be collected for some disease processes such as:

Section 6.9.2. Lymphocyte Subsets, CD4+ and CD8+ - additional protocol reference added.

Original Text:

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to Time and Events schedule (Section 6).

Revised Text:

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to Time and Events schedule (Section 6) and Laboratory Assessments (Section 6.10.2).

Section 6.10.4.1. Definition of an AE – removed duplicate text.

~~The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.~~

Section 6.10.6.1. Treatment Interruption Due to an Adverse Event – clarification provided.

Original Text:

IP and background NRTIs should be restarted as soon as medically appropriate; in general, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist).

Revised Text:

IP and background NRTIs should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist).

Section 6.10.6.14.1. Essential Patient Information – clarification of brand name.

Original Text:

- In order to avoid restarting abacavir, subjects who have experienced a hypersensitivity reaction should be asked to return any remaining EPZICOM tablets to the Investigator or site staff.
- Subjects, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting EPZICOM as more severe symptoms may recur within hours and may include life-threatening hypotension and death.
- Each subject should be reminded to read the Package Leaflet included in the EPZICOM pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Revised Text:

- In order to avoid restarting abacavir, subjects who have experienced a hypersensitivity reaction should be asked to return any remaining EPZICOM / KIVEXA tablets to the Investigator or site staff.
- Subjects, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting EPZICOM / KIVEXA as more severe symptoms may recur within hours and may include life-threatening hypotension and death.
- Each subject should be reminded to read the Package Leaflet included in the EPZICOM / KIVEXA pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Section 6.11.1. PK Sample Collection – clarification of TMC278 sample at Day 1.

Original Text:

For subjects randomized to GSK744, pre-dose blood samples for evaluation of GSK1265744 (2 mL each) and TMC278 (3 mL ~~each~~) will be collected as described in Table 4.

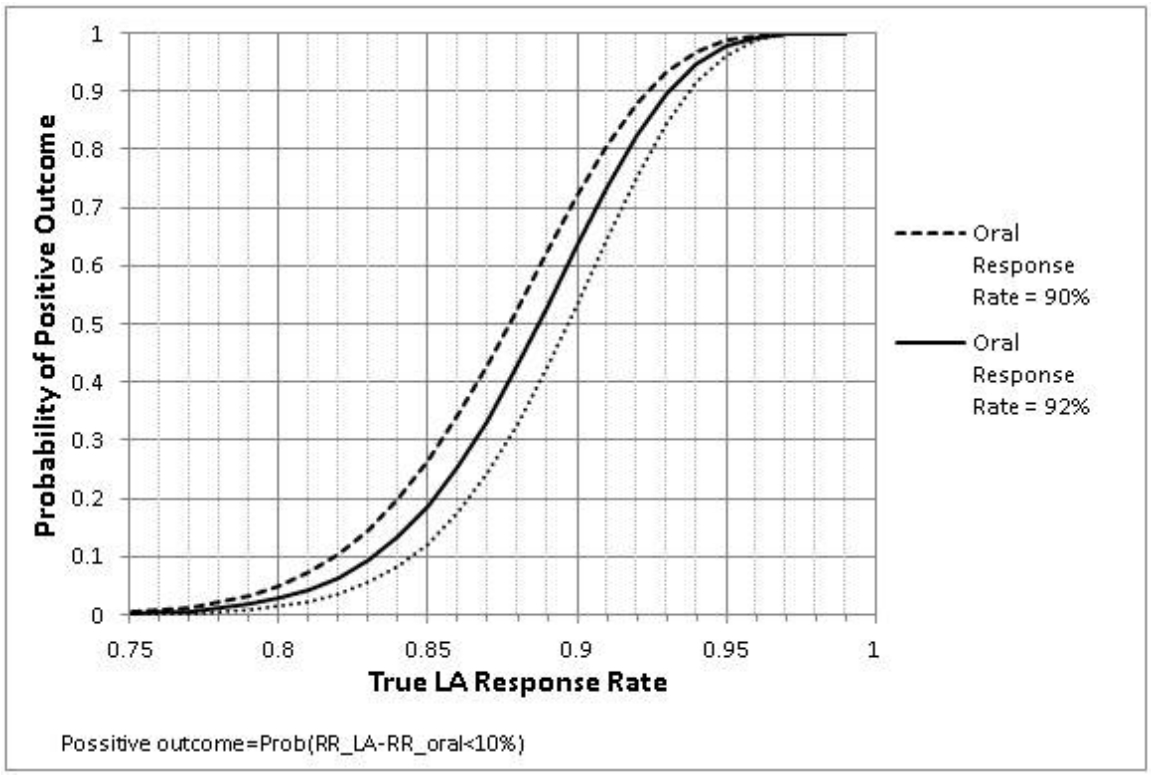
Revised Text:

For subjects randomized to oral GSK744, pre-dose blood samples for evaluation of GSK1265744 (2 mL each) and TMC278 (3 mL, Day 1 predose only) will be collected as described in Table 4.

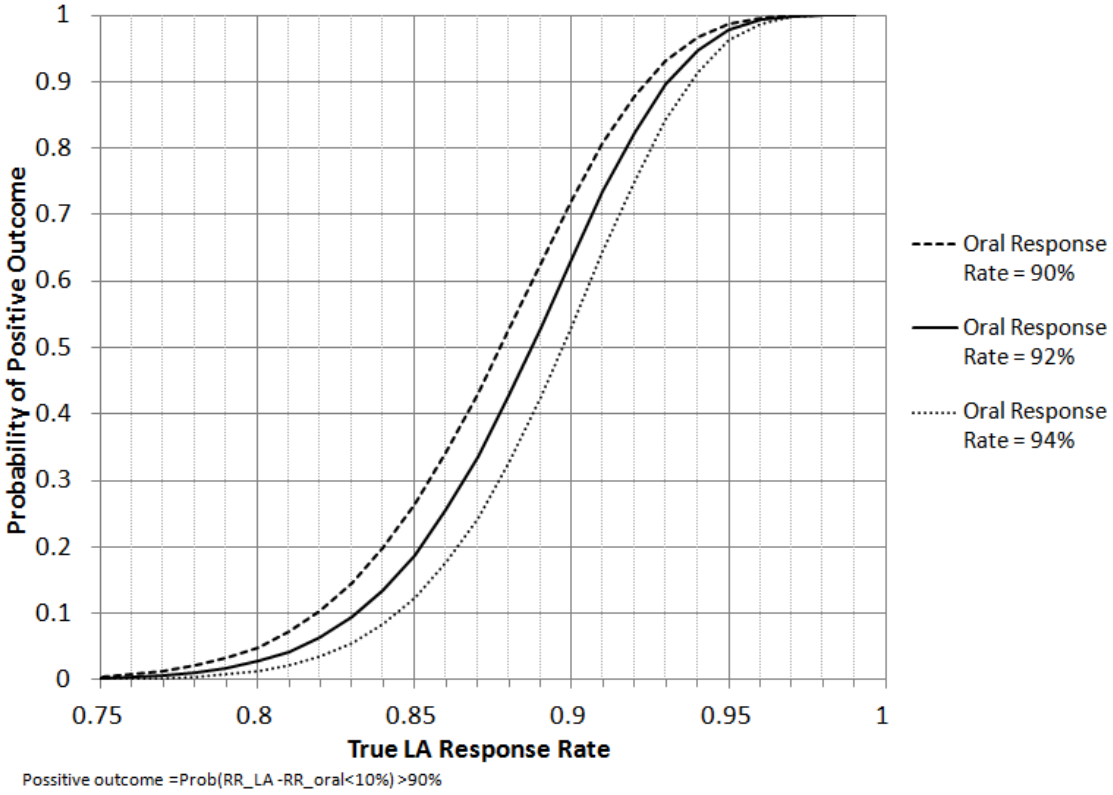
New Text Added: New row in Table 4 showing pre-dose TMC278 collection at Day 1.

Section 8.2.2. Sample Size Sensitivity – Updated Figure 6 legend to include 94% response.

Original Figure:



Revised Figure:



Section 8.3.1.1. Intent-to-Treat Exposed Population (ITT-E) – corrected typo.

Original Text:

The ITT-E population consists of all enrolled subjects who received at least one dose of IP.

Revised Text:

The ITT-E population consists of all enrolled subjects who receive at least one dose of IP.

Section 8.3.1.2. Intent-to-Treat Maintenance Exposed Population (ITT-ME) – corrected typo.

Original Text:

The ITT-ME population consists of all randomized who received at least one dose of IP during the Maintenance Period of the study.

Revised Text:

The ITT-ME population consists of all randomized subjects who receive at least one dose of IP during the Maintenance Period of the study.

Section 8.3.1.4. PK Population – corrected typo.

Original Text:

The PK Population will include all subjects who receive~~d~~ GSK1265744 and / or TMC278 and undergo PK sampling during the study, and provide evaluable GSK1265744 and /or TMC278 plasma concentration data.

Revised Text:

The PK Population will include all subjects who receive GSK1265744 and / or TMC278 and undergo PK sampling during the study, and provide evaluable GSK1265744 and /or TMC278 plasma concentration data.

Section 10. References – Updated.

Added New Reference:

Cohen C, Molina JM, Cahn P, et at. Efficacy and Safety of Rilpivirine (TMC278) Versus Efavirenz at 48 Weeks in Treatment-Naïve HIV-1-Infected Patients: Pooled Results From the Phase 3 Double-Blind Randomized ECHO and THRIVE Trials. *JAIDS*. 2012; 60 (1):33-42.

Updated Date:

Original Text:

Edurant Product Information (rilpivirine) June, 2013.

Revised Text:

Edurant Product Information (rilpivirine) May, 2014.

Original Text:

Epzicom~~/Kivexa~~ Product Information (abacavir/lamivudine) May, 2012.

Revised Text:

Epzicom Product Information (abacavir/lamivudine) May, 2012.

Removed duplicate reference:

GlaxoSmithKline Document Number 2011N112455_03: LAI115428 A Randomized, Open Label Study to Investigate the Safety, Tolerability and Pharmacokinetics of Repeat Dose Administration of Long-Acting GSK1265744 and Long-Acting TMC278 Intramuscular and Subcutaneous Injections in Healthy Adult Subjects. Effective Date: 04Feb2013.

Amendment 4

Amendment 4 applies to all countries.

Amendment 4 was prepared to add the collection of a 2-hour post dose PK sample and 2-hour post dose ECG at Week 32 and Week 48. There is no observed safety issue, however, preliminary PK data preceeding IDMC review #1 revealed two subjects with very high 2-hour post dose concentrations of TMC278. A thorough review of all data did not uncover a rationale for this elevation. The additional 2-hour post dose PK samples will be collected to better understand and characterize the PK profile at a few early timepoints. The post dose ECGs should help to monitor for potential ECG changes post dose as there is documentation of some QTc prolongation at higher concentrations of TMC278 which theoretically could occur on this study. Although nothing has been observed to date on either study LAI116482 or 200056.

At the time of the development of the Amendment, Week 96 data from LAI116482 was available and therefore included for informational purposes.

A more detailed description of how injection site reactions has been included for clarity.

Removed “preliminary” or “ongoing” when describing studies that are now complete.

Finally, several miscellaneous clarifications were made throughout.

Authors

Original authors:

Author (s): PPD (physician lead and medical monitor); PPD (project statistician), PPD (study statistician); PPD (pharmacologist); PPD (virologist); PPD (clinical scientist), PPD (pharmacokineticist); PPD (pharmacokineticist); PPD PPD (medical development lead); PPD (operations)

Revised to:

Author (s): PPD (physician lead and medical monitor); PPD (project statistician), PPD (study statistician); PPD (pharmacologist); PPD (virologist); PPD (clinical scientist), PPD (pharmacokineticist); PPD (medical development lead); PPD (operations)

Sponsor Information

Changed the medical monitor’s affiliation from GlaxoSmithKline to ViiV Healthcare. The medical monitor’s contact information remains the same, including the email address.

Changes underlined and struckthrough:

Sponsor Medical Monitor Contact Information:

PPD MD, MPH
ViiV Healthcare
~~GlaxoSmithKline~~
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: PPD
Fax: PPD
e-mail: PPD

Sponsor Serious Adverse Events (SAE) Contact Information:

PPD MD, MPH
ViiV Healthcare
~~GlaxoSmithKline~~
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: PPD
Fax: PPD
e-mail: PPD

Protocol Synopsis

Added:

At one-week post dose visits (Week 1, Week 25, and Week 41), there is no defined visit window, rather visits should occur approximately 1 week from the last injection.

Visits in Long Term Follow Up are to occur as projected from the last injection with a (+ or -) 3 day visit window, from the projected visit date.

Added:

Visits in Long Term Follow Up are to occur as projected from the last injection with a (+ or -) 3 day visit window, from the projected visit date.

Added under Key Study Assessments (changes underlined):

- PK assessments including 2 hour post dose samples at Day 1, Week 32 and Week 48

Section 1.4 GSK1265744 – Long Acting Injectable (GSK744 LA)

Revised to (changes struck through and underlined):

GSK744 LA, a long acting injectable formulation of GSK1265744, has been dosed in 136 healthy subjects. Subjects have received single or repeat doses of GSK744 LA at doses between 100 to 800 mg, either intramuscularly (IM) or subcutaneously (SC) and either alone or in combination with TMC 278 LA (~~completed~~ study LAI114433 [single dose LA, n=58], ~~ongoing~~ study LAI115428 [repeat dose LA, n=40], and ~~ongoing~~ study LAI116815 [single dose LA, n=38]). The adverse event (AE) profile has been similar to those of GSK744 (oral). To date, no studies in HIV-1 infected subjects have been conducted with GSK744 LA.

GSK744 LA has been generally well-tolerated as either an IM or SC dose. Intramuscular injection site reactions (ISRs) have been predominantly mild or Grade 1 (85%), self-limited, and have not led to study discontinuation in any subject to date. Erythema, nodules, induration, and warmth at the injection site were most commonly reported in healthy subjects. Painless nodules were more common following SC injections than IM injections. No treatment emergent serious AEs have been reported in any of the healthy volunteer studies involving GSK744 LA. [~~Preliminary data from ongoing study~~ LAI115428 GlaxoSmithKline Document Number 2011N112455_03 and GlaxoSmithKline Document Number RM2010/00179/04: LAI114433].

Section 1.7 Study LAI116482

Revised to (changes struck through and underlined):

LAI116482 is an ongoing Phase IIb dose-ranging study (GSK744 10 mg, 30 mg, 60 mg) evaluating the utility of a two-drug, two-class combination (GSK744 + RPV) when both are given as a once daily oral regimen following induction of virologic suppression using GSK744 plus 2 investigator selected NRTIs. Eligible subjects enter Maintenance at Week 24 where they begin the GSK744 + RPV regimen.

To date, the study has enrolled 244 subjects, 181 of whom received one of three oral dose regimens of GSK744 (10 mg, 30 mg or 60 mg) plus 2 NRTIs. A planned Week ~~48~~ 96 (24 weeks on Induction and ~~24~~72 weeks on two-drug Maintenance) analysis is complete and demonstrated similar antiviral activity across the three dosing arms of GSK744 in combination with RPV, which compared favorably to the control regimen of EFV 600 mg once daily plus 2 NRTIs.

Rates of protocol defined virologic failure (PDVF) through Week ~~48~~ 96 were low across all study arms. Three subjects receiving GSK744 (one at each dose) and three subjects receiving EFV were characterized as PDVFs during Induction. During Maintenance, ~~two~~ three subjects receiving GSK744 (10 mg, n=2; and 30 mg, n=1) and ~~one~~ two subjects receiving EFV were characterized as PDVF.

During Maintenance, treatment emergent integrase inhibitor (INI) (Q148R) and NNRTI (E138Q) resistance mutations were identified in one ~~of the~~ subject~~s~~ on GSK744 (10 mg). The subject experienced suspected virologic failure (SVF) at Week 48, which was

subsequently confirmed. There was no change in RPV susceptibility, and a 3.08 fold change in susceptibility to GSK744. The subject reported starting an extreme low calorie diet prior to SVF. Week 26 and Week 36 RPV pre-dose concentrations for the subject were lower than concentrations seen in the Phase III RPV studies. The subject also had lower GSK744 predose concentrations in Maintenance compared to Induction. The Week 40 and Week 48 PK for this subject was consistent with Maintenance Phase Individual Average pre-dose values determined prior to the reported dates of calorie restriction.

One subject on GSK744 (10 mg) developed treatment emergent NNRTI resistance NNRTI (K101K/E and E138E/A). The subject experienced virologic failure at Week 72 which was subsequently confirmed. There was no change to GSK744 susceptibility, and a 4.6 fold change in susceptibility to TMC278. There was no treatment-emergent integrase resistance.

By Week 16 or at time of IP discontinuation if before Week 16, 63% of subjects were treated with Truvada (tenofovir/emtricitibine, TDF/FTC) as their background dual NRTI and 37% of the subjects were treated with EPZICOM/KIVEXA™ (abacavir/lamivudine, ABC/3TC). Similar virologic response rates (HIV-1 RNA < 50 c/mL) through 24 weeks were seen in subjects taking GSK744 + ABC/3TC (87%) and in subjects taking GSK744 + TDF/FTC (86%). ~~Rates continued to be similar through Week 48, 79% for subjects taking GSK744 + ABC/3TC and 84% in subjects taking GSK744 + TDF/FTC.~~

Following induction therapy, GSK744 + RPV (86%) maintained virologic suppression at a rate similar to EFV + NRTIs (83%) through 96 weeks. There was a numerically lower response rate of GSK744 10 mg and GSK744 30 mg, relative to GSK744 60 mg, but this was largely due to non-virologic discontinuations, with a low PDVF rate across all arms.

The most common treatment-emergent AEs reported for subjects on any of the GSK744 doses, were upper respiratory tract infections, diarrhea, nausea, and headache. One subject receiving GSK744 60 mg and one subject receiving GSK744 30 mg had a Grade 3 headache. The Grade 3 headache for the GSK744 60 mg subject occurred very early, study day 3, while the Grade 3 headache for the GSK744 30 mg subject occurred on study day 343. ~~All other AEs were Grade 1 or 2 with the majority of them being Grade 1.~~ The majority of AEs were Grade 1 (29%) or Grade 2 (49%) severity. ~~Six~~ Seven subjects on GSK744 versus ~~eight~~ nine on EFV withdrew due to an AE, one receiving 10 mg (ECG abnormal and palpitations), ~~one~~ two receiving 30 mg (panic attack, Burkitt's lymphoma) and four receiving 60 mg (hepatitis, transaminases increased, anxiety disorder and musculoskeletal pain). The majority of GSK744 related AEs were Grade 1 and few of those AEs led to withdrawal through Week ~~48~~ 96 (n=4 [2%]). There have been no GSK744 drug related SAEs to date.

Two of the subjects that withdrew due to AE met liver stopping criteria with an alanine aminotransferase (ALT)>10x upper limit of normal (ULN) at approximately Week 4 and Week 8 after initiating study drug. Both had pre-existing steatohepatitis and were dosed with GSK744 60 mg + ABC/3TC. Both subjects remained asymptomatic, had normal serum bilirubin levels and had resolution of the ALT values after drug discontinuation. These 2 subjects ~~were~~ accounted for the only Grade 3-4 ALT abnormalities in this study

to date. Overall, the rates of any graded ALT or aspartate aminotransferase (AST) abnormality were similar between GSK744 and EFV dosed subjects through Week ~~48~~ 96: ALT: ~~17~~ 20% and 21% respectively; AST: 25~~0~~% and ~~18~~21% respectively.

These data from LAI116482 support the conduct of study 200056 by demonstrating the antiviral activity of GSK744 when used initially as part of a HAART regimen to induce virologic suppression. In addition, this data confirmed antiviral activity of GSK744 + RPV as a two-drug oral Maintenance regimen and provides proof of principle for GSK744 LA + TMC278 LA as a maintenance regimen.

Based upon the results through Week ~~48~~ 96 of the LAI116482 study [Margolis, 2015], and in accordance with the pre-specified dose selection criteria at Week ~~24~~48, a 30 mg oral dose of GSK744 has been selected to be used in combination with ABC/3TC for induction of virologic suppression in study 200056.

All ongoing subjects in the LAI116482 study have entered ~~into Maintenance~~ the Open Label Extension phase to continue to receive the two drug regimen of GSK744 30 mg + RPV 25 mg ~~where they have completed 24 weeks or more of the two-drug Maintenance regimen~~. All subjects ~~will have~~ had completed 48 weeks of the Maintenance regimen ~~at~~ by the time study 200056 ~~begins~~ began dosing any IM regimen, permitting a robust evaluation of the virologic efficacy of the oral two drug regimen of GSK744 and RPV, prior to initiating the long acting injectable regimen. These data will be made available to Investigators.

Section 1.10.1 Risk Assessment

Section 1.10.1.1 GSK744 and GSK744 LA

Added:

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that GSK744 LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of GSK744 LA. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type.

Mitigation: Training will be provided to all sites on proper injection technique. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of GSK744 concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of GSK744 and TMC278 concentrations.

Section 1.10.1.3 TMC278 LA

Added:

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that TMC278 LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of TMC278 LA. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type.

Mitigation: Training will be provided to all sites on proper injection technique. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of TMC278 concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of GSK744 and TMC278 concentrations.

Section 1.10.1.6 Efficacy Risk

Changed title of section to "Risk of Treatment Failure"

And added:

Due to administrationor error, it is possible that a subject could receive an inadequate dose of GSK744 LA or TMC278 LA. Sub-therapeutic concentrations of either GSK744 LA or TMC278 LA could lead to virologic failure and possibly the development of resistance. HIV-1 RNA viral loads will be closely monitored throughout the injection period of the study.

Section 1.10.2 Benefit Assessment

Last sentence updated to be through Week 96.

Revised to (changes struckthrough and underlined):

Efficacy of the two-drug regimen, as oral agents, has been demonstrated through Week ~~48~~ 96 of the ongoing LAI116482 study.

Section 3.3 Discussion of Design

Added study number to Table 3.

Revised to (changes underlined):

Table 10 LAI116482 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-ME Population)

Visit	GSK744 10 mg N=52 n (%)	GSK744 30 mg N=53 n (%)	GSK744 60 mg N=55 n (%)	GSK744 Subtotal N=160 n (%)	EFV 600 mg N=47 n (%)
Week 16 - Induction	50 (96)	49 (92)	52 (95)	151 (94)	43 (91)
Week 24 - Induction	50 (96)	50 (94)	53 (96)	153 (96)	45 (96)
Week 48 - Maintenance	48 (92)	48 (91)	53 (96)	149 (93)	44 (94)

Section 4.5 Withdrawal Criteria

Clarified that the change from Baseline QT criteria is an increase in QTc > 60 msec.

Revised to (changes underlined):

- The following QT criteria:
  - QTc >500 msec
  - Uncorrected QT >600 msec
  - Change from Baseline: Increase in QTc > 60 msec

Section 5.1.7 Dosing Considerations for GSK744 LA + TMC278 LA

Clarified need for varied needle lengths and added language regarding maladministration.

Revised to (changes struckthrough and underlined):

Variable needle lengths may need to be used to accommodate individual body type. For example, longer needle lengths ~~will~~ may be required for subjects with higher body mass indexes (BMIs, example > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. BMI and needle length used will be collected in the eCRF.

Added:

Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the subject stay onsite for up to 2 hours post dose for safety monitoring and notifying the medical monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of GSK744 and TMC278 concentrations.

Section 5.7.1 Oral Dosing

Revised section heading to "Oral Dosing Including Long Term Follow Up."

Added:

Visits for subjects in Long Term Follow Up are expected to occur as projected according to the last injection. There is a (+ or -) 3 day visit window, from the projected visit date.

Section 5.7.2 IM Dosing

Clarified visit window for one week post dose visits.

Revised to (changes underlined):

IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred. At one-week post dose visits (Week 1, Week 25, and Week 41), there is no defined visit window, rather visits should occur approximately 1 week from the last injection.

Section 5.11 Treatment of Study Treatment Overdose

Added:

Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the subject stay onsite for up to 2 hours post dose for safety monitoring and notifying the medical monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of GSK744 and TMC278 concentrations.

Section 6.2 Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q8W)

Added a footnote "c" to ECG line at Week 32 and 48. Added a footnote "k" to PK line at Week 32 and 48.

Procedures For Maintenance – **Q8W** regimen	D1	W1	W4	W8	W12	W16	W20	W24	W25	W28	W32	W36	W40	W41	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	WD[p, q]
ECG[c]	X[pre]	X	X	X				X			X[c]					X[c]				X				X			X	X
PK Sample (S)torage[k]	X[k]	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X	X[k]		S		S		S		S		S		S	X

Revised footnote "c" to (changes underlined):

c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit. At Week 32 and Week 48, a second ECG will be obtained approximately 2 hours after the last injection and just prior to the 2 hour post dose PK sampling.

Revised footnote "k" to (changes underlined):

k) Take PK samples pre-dose except Weeks 1, 12, 20, 25, 28, 36, 41 and 44 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of GSK744+ABC/3TC+RPV. A second Day 1, Week 32 and Week 48 PK sample will be collected approximately 2 hours after the last injection.

Section 6.3 Time and Events Table – Maintenance Period for IM Regimen (GSK744 LA + TMC278 LA Q4W)

Added a footnote "c" to ECG line at Week 32 and 48. Added a footnote "k" to PK line at Week 32 and 48. Added table title to first cell. Changes underlined.

Procedures For Maintenance – **Q8W** regimen	D1	W1	W4	W8	W12	W16	W20	W24	W25	W28	W32	W36	W40	W41	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	WD[p, q]
ECG[c]	X[pre]	X	X	X				X			X[c]					X[c]				X				X			X	X
PK Sample (S)torage[k]	X[k]	X	X	X	X	X	X	X	X	X	X[k]	X	X	X	X	X[k]		S		S		S		S		S		S	X

Revised footnote "c" to (changes underlined):

c) 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, the ECG may be done at any time during the visit. At Week 32 and Week 48, a second ECG will be obtained approximately 2 hours after the last injection and just prior to the 2 hour post dose PK sampling.

Revised footnote "k" to (changes underlined):

k) Take PK samples pre-dose except Weeks 1, Week 25 and Week 41 which can be taken at any time during the visit. Day 1 PK sample should be taken after review of PK diary and pre-dose of GSK744+ABC/3TC+RPV. A second Day 1, Week 32 and Week 48 PK sample will be collected approximately 2 hours after the last injection.

Section 6.7 Time and Events Table – Long-Term Follow Up Period

Missing footnote "c". Added (underlined):

Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [g]					X	X

Section 6.9.1 Plasma HIV-1 RNA

Revised last sentence to (changes struckthrough and underlined):

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 6). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases (e.g., where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods ~~may~~will be used to further characterize HIV-1 RNA levels.

Section 6.10.1 Clinical evaluations

Clarified injection site reaction evaluations.

Added:

The investigator should utilize subject diary reports to assist with a clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale). A clinical assessment should be performed both before and after an injection to identify resolving and new ISRs. The clinical assessment and interpretation of any ISR, including those reported by the subject via diary, will be documented in the ISR AE eCRF. Daily diary data, or subject assessment, will be documented verbatim in the diary eCRF.

Section 6.10.2 Laboratory Assessments, Section 6.10.3.2 Liver Chemistry Stopping Criteria, Subject Management and Section 6.12 Viral Genotyping and Phenotyping

Changed "Quest Diagnostics" to "central laboratory" throughout.

Section 6.10.2 Laboratory Assessments

Removed reference to Cockgroft-Gault formula as Creatinine Clearance may be derived by another formula. Changes to footnote struck through.

b) Creatinine clearance will be estimated by the central laboratory ~~using the Cockcroft-Gault method [Cockcroft, 1976]~~ and assessed at Screening, Baseline, Week (-12), Week (-4), Day 1 and Weeks 4, 16, 32, 48 and 96.

Removed erroneous footnote "h".

Section 6.10.4.1 Definition of an AE

Added as an event meeting the definition of AE:

- All injection site reactions.

Section 6.10.6.11 QTc Prolongation

Clarified instances when IP should be discontinued.

Revised to (changes underlined):

Subjects with an average QTc interval > 500 msec or a >60 msec increase from baseline, from three or more tracings separated by at least 5 minutes should have IP discontinued.

Section 6.10.6.12 Injection Site Reactions (ISRs)

Clarified that ISRs will be managed through investigator assessment and subject diaries. Combined this section with original Section 6.10.11 Injection Site Reaction Monitoring.

Revised to (changes struckthrough and underlined):

Injection site reactions will be managed through ~~AE reporting and patient~~ investigator assessment and subject diary collection throughout the study. All Grade 3 or 4 ISRs must be discussed with the medical monitor to determine etiology and assess appropriate continued study participation.

Digital photographs will be documented where possible on all subjects who have an injection site reaction that is either serious or Grade 2 or above that persist beyond 2 weeks. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.

ISR discomfort can be managed symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the subject's ability to perform activities of daily living. The required intervention should be documented on the appropriate eCRF page.

Section 6.10.11 Injection Site Reaction Monitoring

Deleted this section and combined with Section 6.10.6.12.

~~Subjects on either IM regimen will be monitored closely both clinically and by patient report for the following in relation to injection site reactions:~~

~~• Pain, tenderness, pruritis, warmth, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).~~

~~Digital photographs will be documented where possible on all subjects who have an injection site reaction that is either serious or Grade 2 or above that persist beyond 2~~

~~weeks. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.~~

~~Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.~~

Section 6.11.1 PK Sample Collection

Updated PK sampling Table 4 to include a 2 hour post dose sample for GSK1265744 and TMC278 at Week 32 and Week 48.

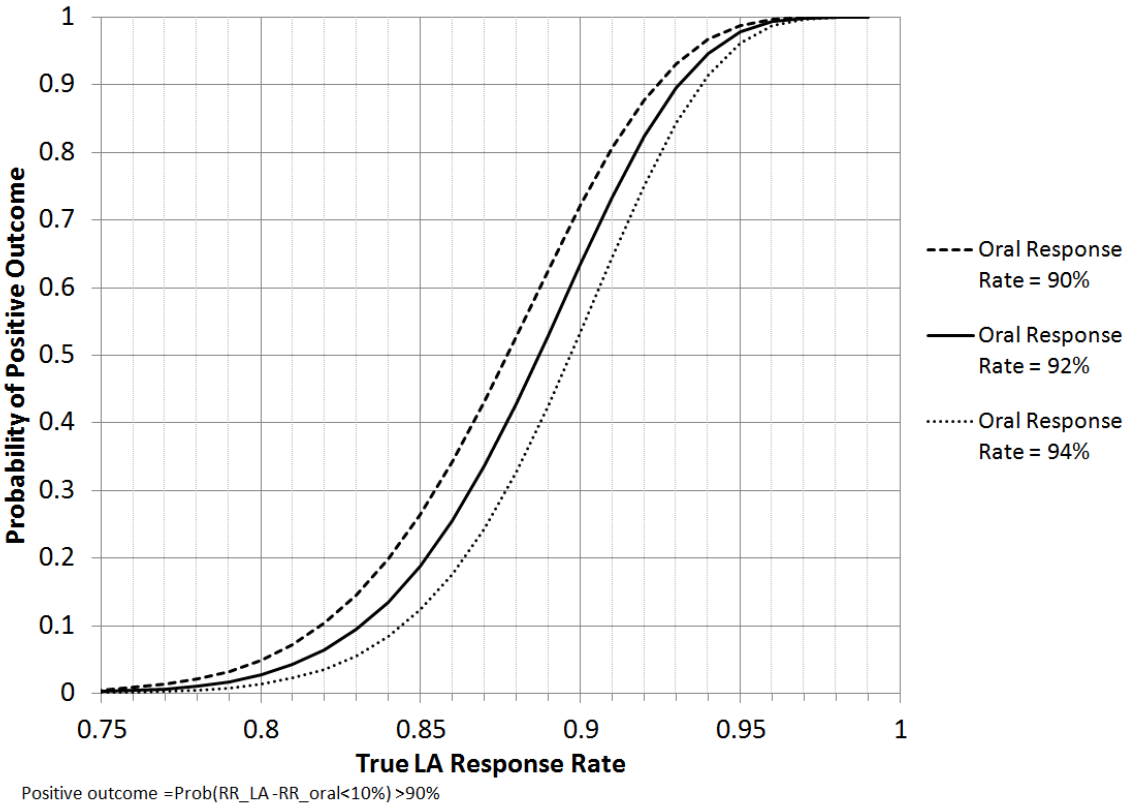
Group	Analyte	Week	Sample Times Relative to Dose
IM	GSK1265744	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40 and 48 Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1, Week 32 and Week 48 1 Week Post Dose: Week 1, Week 25 and Week 41 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
	TMC278	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40 and 48 Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose: Day 1, Week 32 and Week 48 1 Week Post Dose: Week 1, Week 25 and Week 41 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
Oral	GSK1265744	Day 1, Weeks: 32 and 48	Pre-Dose: Day 1, Weeks 32 and 48
	TMC278	Day 1	Pre-Dose: Day 1

Section 6.11.1 PK Sample Collection and Section 6.11.3 Bioanalysis of GSK1265744 and TMC278

Removed reference to SPM. All PK sampling details are in the central laboratory manual.

Section 8.2.2 Sample Size Sensitivity

Corrected spelling of "positive" in Figure 6.



Section 8.3.1.3 Per Protocol Maintenance Population

Clarified this as the Maintenance Exposed Population. Changed section title to "Per Protocol Maintenance Exposed Population (PP-ME)."

Revised to (changes underlined):

The PP-ME population will be a secondary population for efficacy purposes.

Section 8.3.3.1 Primary Comparisons of Interest

Corrected response rate.

Revised to (changes struckthrough and underlined):

The probability of (Response rate for IM arm ~~≤~~ ≥ Response rate for Oral arm -10%) will be calculated.

Section 8.3.4.1 IDMC Interim Analysis

Clairified that the first IDMC analysis may not occur before all subjects enter Maintenance.

Revised to (changes struckthrough and underlined):

The IDMC ~~will~~ intends to review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period, or as soon as reasonably possible after subjects begin to enter the Maintenance Period.

Section 8.3.5.2 Safety Analyses

Clarified that injection site reactions will be part of the AE summaries provided.

Revised to (changes underlined):

Exposure to study medication, measured by the number of weeks on study drug, will be summarized by treatment arm. The proportion of subjects reporting adverse events (AEs) will be tabulated for each treatment arm. The following summaries of AEs will be provided:

Incidence and severity of All AEs including injection site reactions;

References

Added:

Margolis, D, et al. Cabotegravir and Rilpivirine As Two-Drug Oral Maintenance Therapy: LATTE Week 96 Results. 22nd Conference on Retroviruses and Opportunistic Infections; February 23-26, 2015 Poster 554LB

Amendment 5

General

Clarifications of naming conventions of cabotegravir and rilpivirine (both formulations) were made throughout to document to be in line with the defined terms in Section 1.2. In addition, the Extension Period was revised throughout the document to allow subjects to remain on their randomized IM regimens (rather than switching to a single selected IM regimen as originally planned), and to allow subjects randomized to the oral arm in the Maintenance Period to switch to one of the optimized Q8W/Q4W regimens, based on subject preference

Week 32 and 48 data from 200056 was added.

Various clarifications made throughout the document.

Protocol Synopsis

The Extension Period and IDMC sections were modified to reflect the new design. Most sections had minor revisions.

Section 1.8 200056

Section added to Protocol.

The 200056 study (LATTE-2) evaluated a 20 week induction of HIV-1 RNA suppression with a three drug oral antiretroviral regimen consisting of CAB + ABC / 3TC Fixed Dose Combination (FDC) followed by randomization to a two-drug regimen consisting of intramuscular (IM) long-acting (LA) CAB LA + RPV LA compared to continuation of oral CAB + ABC / 3TC for the maintenance of HIV-1 RNA suppression. A total of 309 participants were enrolled and treated.

During the Induction Period there was a rapid and sustained decline in HIV-1 RNA, with 91% of participants (282/309) achieving HIV-1 RNA <50 c/mL through 20 weeks of therapy. There was a single participant (with known compliance issues) with confirmed virologic failure during the Induction Period. Virologic testing revealed no treatment emergent phenotypic or genotypic resistance in this participant.

The primary endpoint for 200056 was the Week 32 proportion of participants with HIV-1 RNA < 50 c/mL (Snapshot, Intent-to-Treat Maintenance Exposed population [ITT-ME]). Following virologic suppression on three drug oral therapy in the Induction Period, 286 participants qualified to enter randomization at the Day 1 visit, and were subsequently randomized 2:2:1 onto every 4 week intramuscular (IM) injections with CAB LA + RPV LA (Q4W), every 8 week IM injections with CAB LA + RPV LA (Q8W) or continuation of oral CAB + NRTIs, respectively. At the time of randomization at Day 1, participants entering one of the IM arms discontinued all oral ART. Through 32 weeks of two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes, compared to 91% of participants

continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms. Through 32 weeks of Maintenance therapy, there was one participant each on Q8W and oral dosing with confirmed virologic failure (CVF), without any evolution of viral resistance. The CVF on Q8W dosing occurred following an aberrant RPV injection, without measurable plasma RPV concentrations 4 weeks post dosing.

Week 48 data was a secondary endpoint for 200056, and permitted the evaluation of the two-drug long-acting combinations' ability to maintain the virologic suppression demonstrated at Week 32. At Week 48, 92% (Q8W) and 91% (Q4W) of participants receiving injectable dosing had a sustained virologic response (HIV-1 RNA <50 c/mL) compared to 89% of participants continuing oral CAB + 2 NRTIs. Although the proportion of participants with virologic success was similar for Q8W and Q4W dosing, the reason for Snapshot failure was different between the arms. There were more Snapshot failures for virologic reasons on the Q8W arm (n=8, 7%) than in the Q4W arm (n=1, <1%), and more participants with no virologic data (discontinued due to AE or other reasons) on the Q4W arm (n=9, 8%) compared to the Q8W arm (n=1, <1%).

Between Week 32 and Week 48, one additional participant (Q8W) had confirmed virologic failure. This participant had a Baseline HIV-1 RNA of 444,489 c/mL. At Week 48, the participant was a suspected virologic failure with HIV-1 RNA = 463 c/mL. Upon retest, ten days later, the virologic failure was confirmed with HIV-1 RNA of 205 c/mL. At the time of CVF, this participant had treatment emergent NNRTI resistance K103N, E138G, and K238T, with high level phenotypic resistance to delaviridine (>MAX), efavirenz (48 fold change [FC]), nevirapine (>Max), and rilpivirine (3.34 FC). The fold change to etravirine (1.91) was below the lower cutoff. Week 48 integrase genotype had the treatment emergent integrase resistance mutation Q148R, with accompanying resistance to raltegravir (29 FC), elvitegravir (138 FC), and cabotegravir (6.06 FC). The Week 48 sample was not resistant to dolutegravir (1.38 FC).

Overall, AEs and clinical chemistries were similar to those observed in prior studies with CAB, without discernible trends between Q8W, Q4W, and oral. Injections were well tolerated with two participants discontinuing due to injection tolerability through 48 weeks (both on Q8W dosing). The vast majority of injection site reactions were due to pain/discomfort with nearly all injection site reactions classified as mild (82%) or moderate (17%), with <1% of reactions classified as severe. There was no discernible tolerability difference between Q4W (2 mL) dosing and Q8W (3 mL dosing). The most common non-ISR AEs during the Maintenance Phase were nasopharyngitis (24%), headache (16%), and diarrhea (13%) on IM arms and nasopharyngitis (30%), headache (11%), and diarrhea (5%) on oral CAB. Through Week 48, SAEs during the Maintenance Period occurred in 7% of participants randomized to CAB LA + RPV LA and 5% of participants randomized to remain on oral treatment, none were drug related. Based on the data from the Week 48 endpoint, Q4W dosing was chosen to progress for further clinical development in Phase 3 studies, however, due to continued interest in evaluating the potential of Q8W dosing, subjects entering the Extension Period from the oral CAB 30 mg + ABC/3TC arm in this study will be given the option to switch to either an optimized Q8W or Q4W regimen. Subjects originally randomized to the IM regimen and entering the extension phase will remain on their randomized regimen.

Section 1.9 Study Rationale

Extension Period revised to (changes struck through and underlined):

The Extension Period of this study will allow for a collection of longer term efficacy and safety and tolerability data from subjects receiving ~~GSK744~~ CAB LA and ~~TMC278~~ RPV LA. ~~Only one~~ Both of the current IM dosing regimens, ~~either Q4W or~~ Q8W and Q4W, will be taken into the Extension Period of the study ~~(~~based on ~~criteria described in the Reporting and Analysis Plan [RAP])~~similar efficacy results across each arm (see Section 1.8)..

Unless subjects meet a study withdrawal criterion, subjects on the oral regimen may elect to continue on the Extension Period by switching to ~~the selected GSK744 LA + TMC278 LA dosing regimen. If eligible, their regimen will be modified prior to entering Extension by adding RPV 25 mg orally once daily for 2 weeks. This short RPV add on will allow eligible subjects to achieve steady state levels of RPV, prior to the administration of the GSK744 LA + TMC278 LA.~~ an optimized IM dosing regimen of their choice of CAB LA + RPV LA (either Q8W or Q4W).

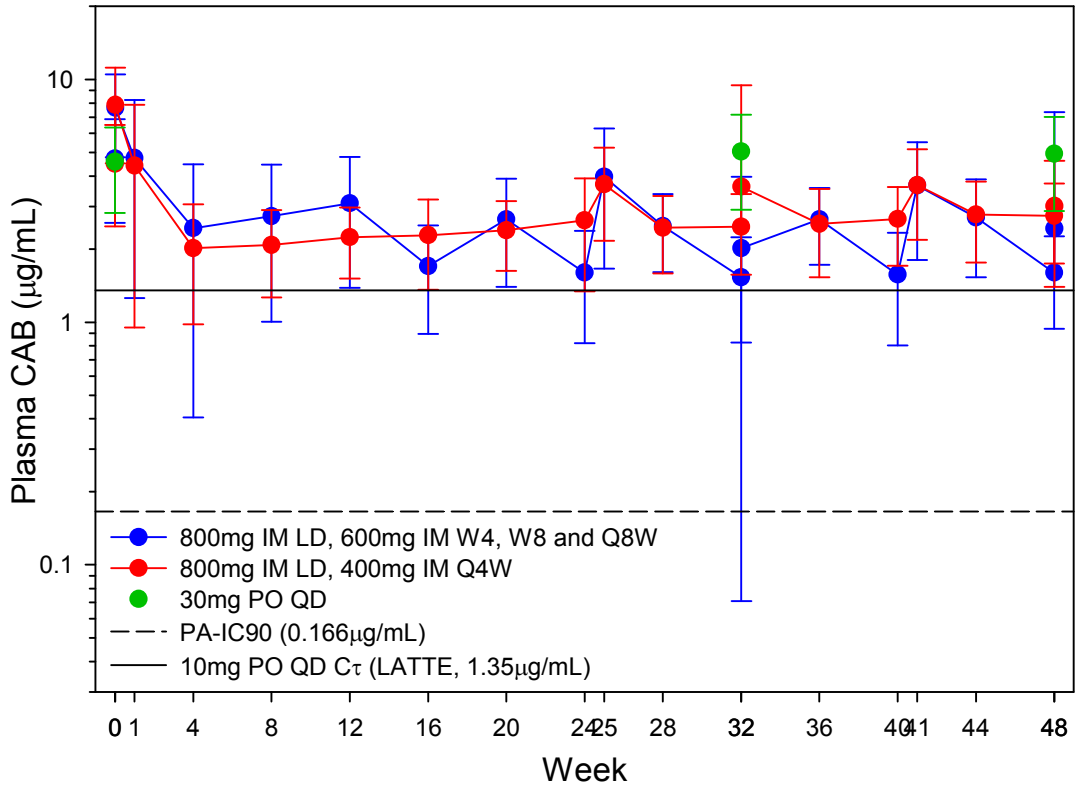
Section 1.10 Dose Rationale

Added the following sections for CAB LA-Extension and RPV LA-Extension:

CAB LA – Extension Period

CAB concentrations following administration of CAB LA Q8W and Q4W during the Maintenance Period of LATTE-2 were lower than predicted by the modelling and simulation in the original protocol, Observed data for both CAB LA regimens in LATTE-2 are presented in Figure 3. The CAB LA population PK model has been updated to include data from Phase 2a/b studies, specifically Study 201120 (CAB LA PrEP) and Study 200056. The current model has increased from 93 subjects to 416 subjects receiving CAB LA single or repeat IM injections. The rationales for the new CAB LA IM dosing regimens are described below.

Figure 3 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 48 (200056, LATTE-2)

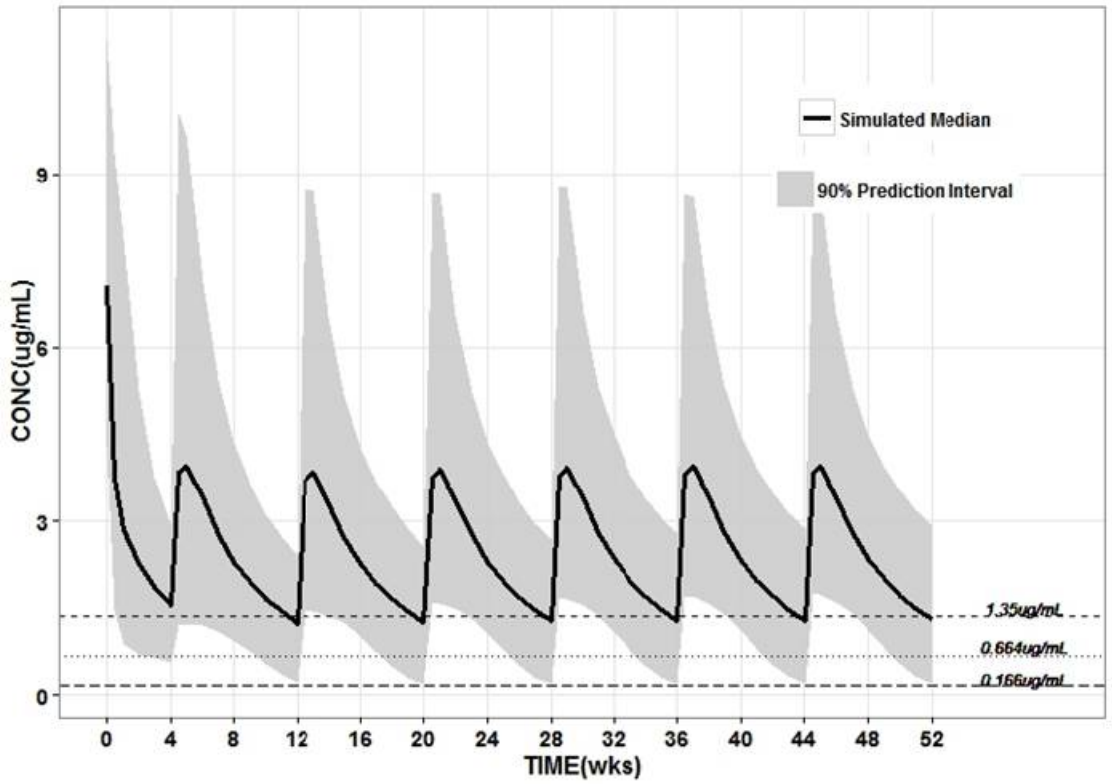


Both predose and 2h post injection concentrations are shown at Time Zero, Week 32, and Week 48.

Extension Phase Rationale for CAB LA Q8W

After the Maintenance Period oral regimen, the first and second CAB LA 600 mg IM dose at study visit Week 100 (1st injection day) and Week 104 (2nd injection) of the Extension Period of this study was selected so that 50% of subjects are anticipated to be above 1.35 µg/mL, the geometric mean Cτ following oral CAB 10 mg once daily, throughout treatment which was shown to be efficacious in the LATTE study. The lower bound of the 90% prediction interval is approximately 0.166 µg/mL, indicating that 95% of subjects on this regimen should remain above the PA-IC_{90} throughout dosing ().

Figure 4 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, Q8W thereafter)^

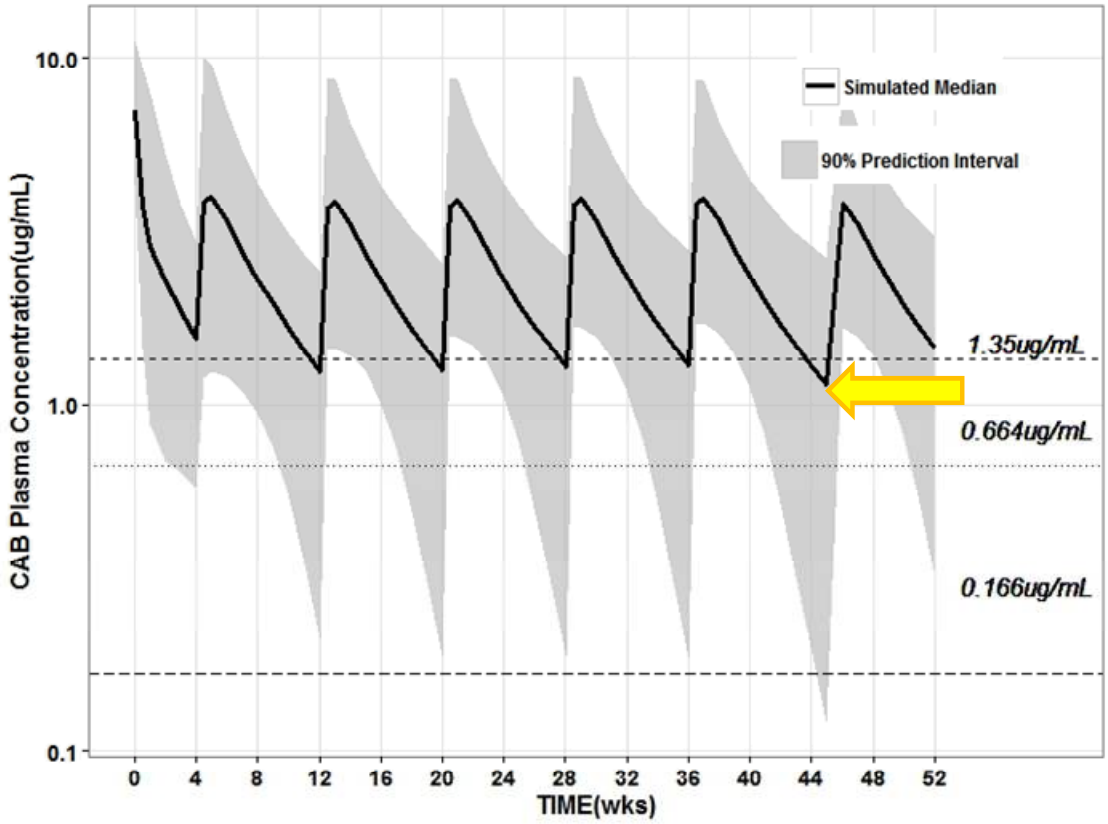


*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Model based predicted steady-state CAB concentrations were consistent with observed data in this study, where CAB LA 600 mg IM Q8W was given, albeit with a loading dose of 800 mg IM on Day 1 and a third dose of 600 mg IM at Week 8 prior to initiating Q8W. The mean CAB plasma concentration at Week 32 was 1.53 μg/mL (Figure 4).

At steady state, a one week delay in dosing of the Q8W regimen is predicted to result in a median steady state Cτ that is 15% lower than for dosing that is administered on schedule, with 92% remaining above the PA-IC_{90} (Figure 5).

Figure 5 Impact of 1-week Delay in Dosing at Steady State (Week 44) on Simulated* Median (90% PI) CAB Plasma Concentrations versus Time for the Optimized CAB LA 600 mg IM Q8W regimen (Day 1, Week 4, and Q8W thereafter^)

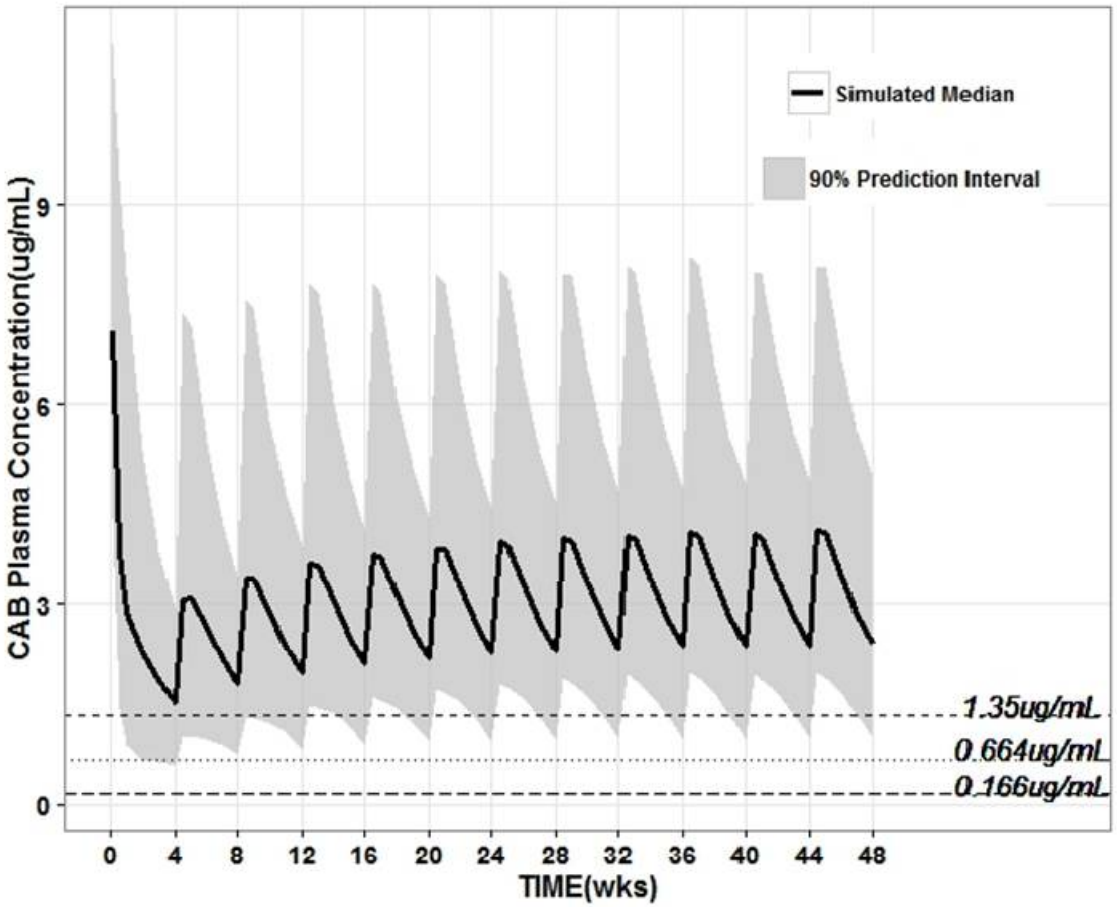


*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Extension Phase Dose Rationale for CAB LA Q4W

The simulation of the predicted median (90% prediction interval [PI]) CAB concentration-time profile based on the population PK model is shown in Figure 6. The lower bound of the PI remains approximately at or above 4x PA-IC_{90} throughout dosing. At steady state, 98% of the population is predicted to achieve trough concentrations above 4x PA-IC_{90}, and 88% is predicted to achieve trough concentrations above the geometric mean trough following the 10 mg oral dose in LATTE of 1.35 µg/mL (8x PA-IC_{90}).

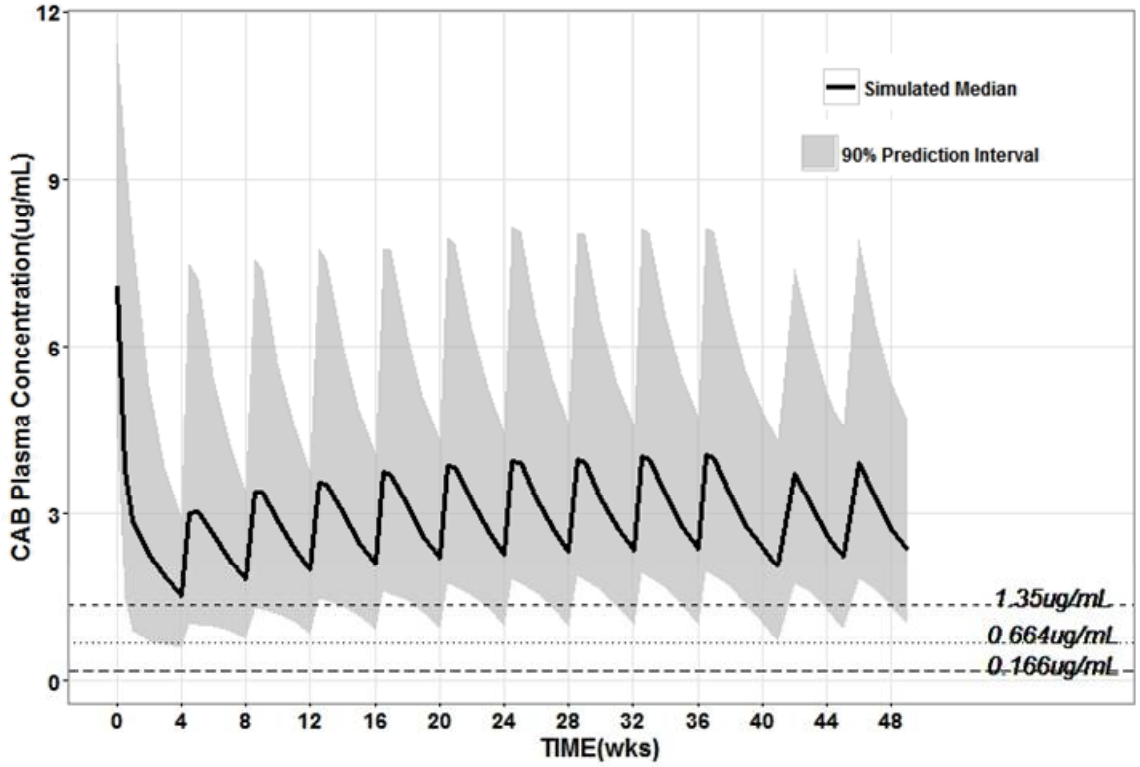
Figure 6 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q4W Regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Ctrough concentration following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC_{90}
Long dashed line at 0.166 μg/mL corresponds to the PA-IC_{90}.

At steady state, a one week delay in dosing of the Q4W regimen results in approximately 15% reduction in median CAB trough. With this delay, 95% are predicted to remain above 4x PA-IC_{90}, and 79% are predicted to remain above the 10 mg oral target (Figure 7). Simulations including delays greater than one week have been explored (not shown), with <70% of subjects remaining above the 10 mg oral target. Therefore, a 1-week delay is the maximum allowed per the protocol.

Figure 7 Impact of 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q4W regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset

^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Cτ following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}

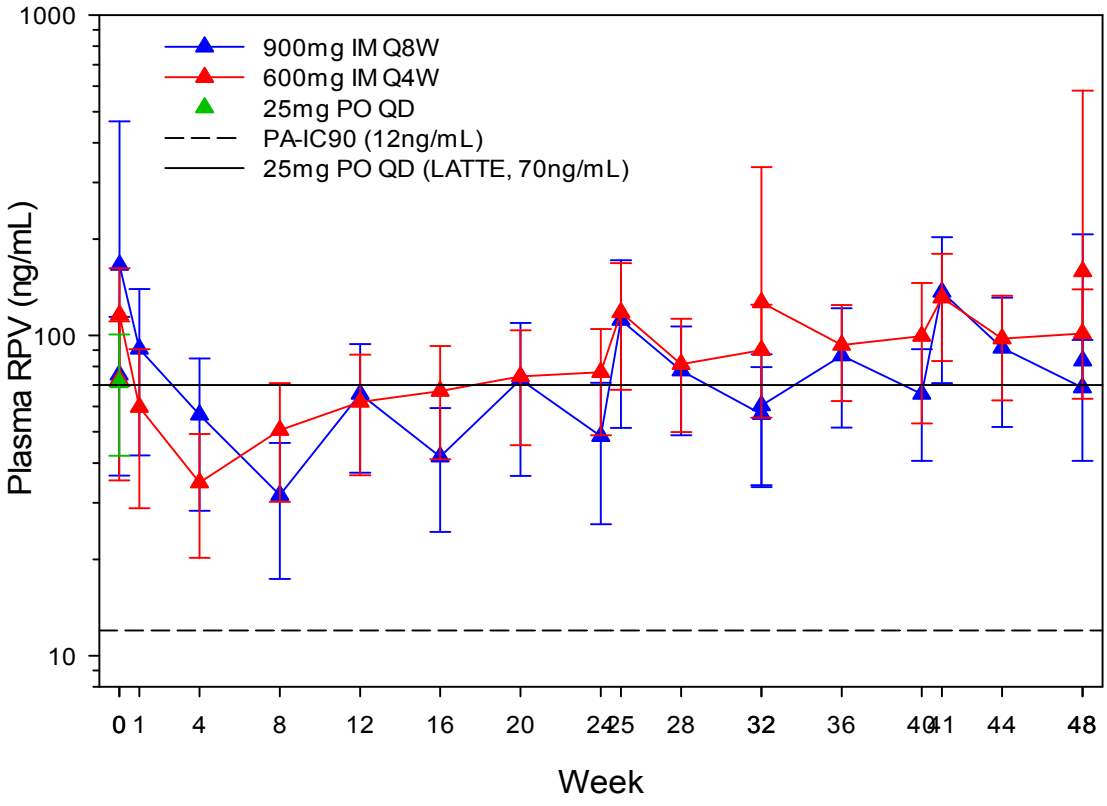
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC_{90}

Long dashed line at 0.166 μg/mL corresponds to the PA-IC_{90}.

RPV LA – Extension Period

Similar to CAB, RPV concentrations following RPV LA in LATTE-2 were lower than predicted by the modelling and simulation in the original protocol. Observed data for both RPV LA regimens in LATTE-2 are presented in Figure 10. The RPV LA population PK model has been updated to include data from LATTE-2.

Figure 10 Observed Mean (SD) Concentration-Time Data following RPV LA Q8W and Q4W through Week 48 and Day 1 Cτ following RPV 25 mg PO QD (LATTE-2)

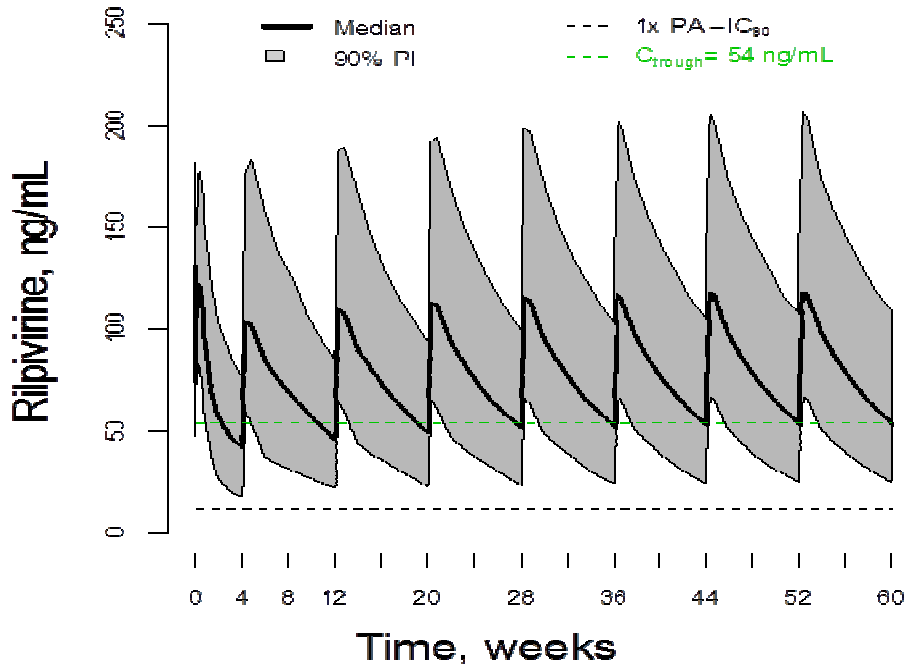


Extension Phase Rationale for RPV LA Q8W

The new optimized RPV LA Q8W regimen for this study was selected based on safety and efficacy data from this study, 200056 (LATTE-2) and supported by modelling and simulation of pharmacokinetic and response data obtained following administration RPV LA administration in healthy subjects (Phase 1 studies C158 and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected subjects (Phase 2 study LATTE-2), the majority of the data coming from 200056 (LATTE-2).

The predicted median (90% PI) steady-state Cτ for the optimized RPV LA Q8W regimen is 54 ng/mL (25 – 109 ng/mL) (Figure 11). With this regimen, 100% of subjects remain above the RPV PA-IC_{90} during the whole dose interval at steady-state. These data are similar to the observed Week 32 median steady-state Cτ which was also 54 ng/mL and the mean Cτ was 58 ng/mL (Figure 10). With the 2nd RPV LA dose at Week 104, the anticipated median RPV Cτ at Week 104 is 42 ng/mL (versus 30 ng/mL observed prior to second injection at Week 8 in LATTE-2), with >98% of subjects above the RPV PA-IC_{90}.

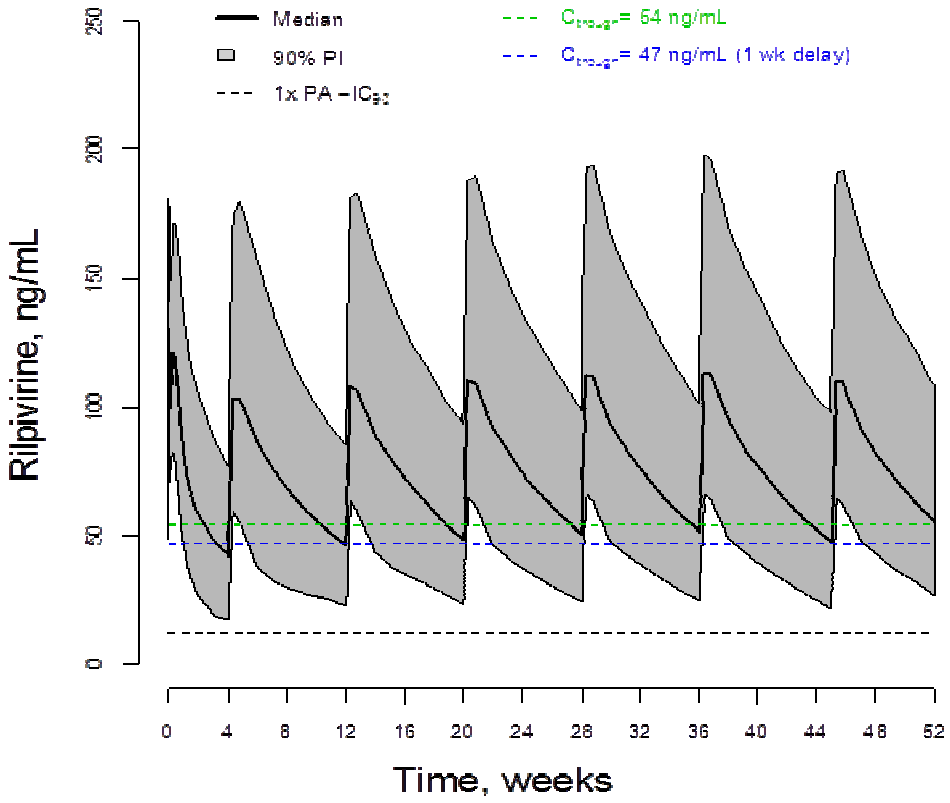
Figure 11 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q8W regimen (900 mg IM Day 1, Week 4, and Q8W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

At steady-state, a one week delay in dosing for the Q8W regimen is predicted to result in a median steady-state Cτ that is approximately 13% lower (47 ng/mL) than for dosing that is administered on schedule, with >99% of subjects still remaining above the RPV PA-IC_{90} (Figure 12). This supports allowance of some flexibility in the dosing regimen in this study, similar to what is currently practiced in this study.

Figure 12 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for Optimized RPV LA Q8W dosing regimen, impact of 1-week visit window (injection at Week 45 instead of Week 44)^



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

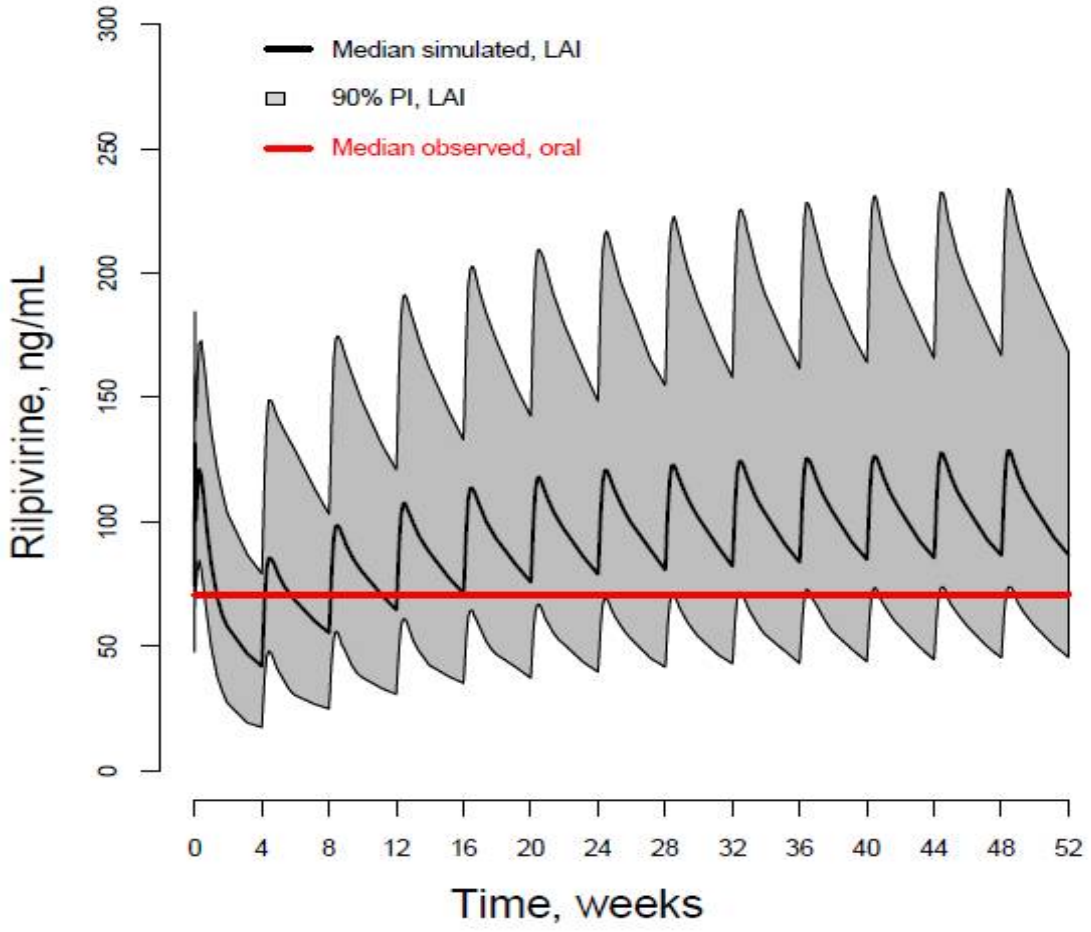
Extension Phase Rationale for RPV LA Q4W

The optimized RPV LA Q4W regimen for this study was selected based on LATTE-2 safety and efficacy data as described above and supported by modeling and simulation of pharmacokinetic data obtained following administration of RPV LA in healthy participants (Phase 1 studies C158 and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected participants (Phase 2 study LATTE-2), with the majority of the data coming from 200056 (LATTE-2).

The predicted median (90% PI) steady-state Cτ for the proposed regimen is 86.8 ng/mL (45.6 – 168 ng/mL) (Figure 13). With this regimen, >99% of participants remain above the 5th percentile of steady state trough values following oral RPV 25 mg (corresponding to 2x the PA-IC_{90}). With a loading dose of 900 mg RPV LA on Day 1, the anticipated

median RPV Cτ at Week 4 is 42 ng/mL, with >98% of participants above the RPV PA-IC_{90}.

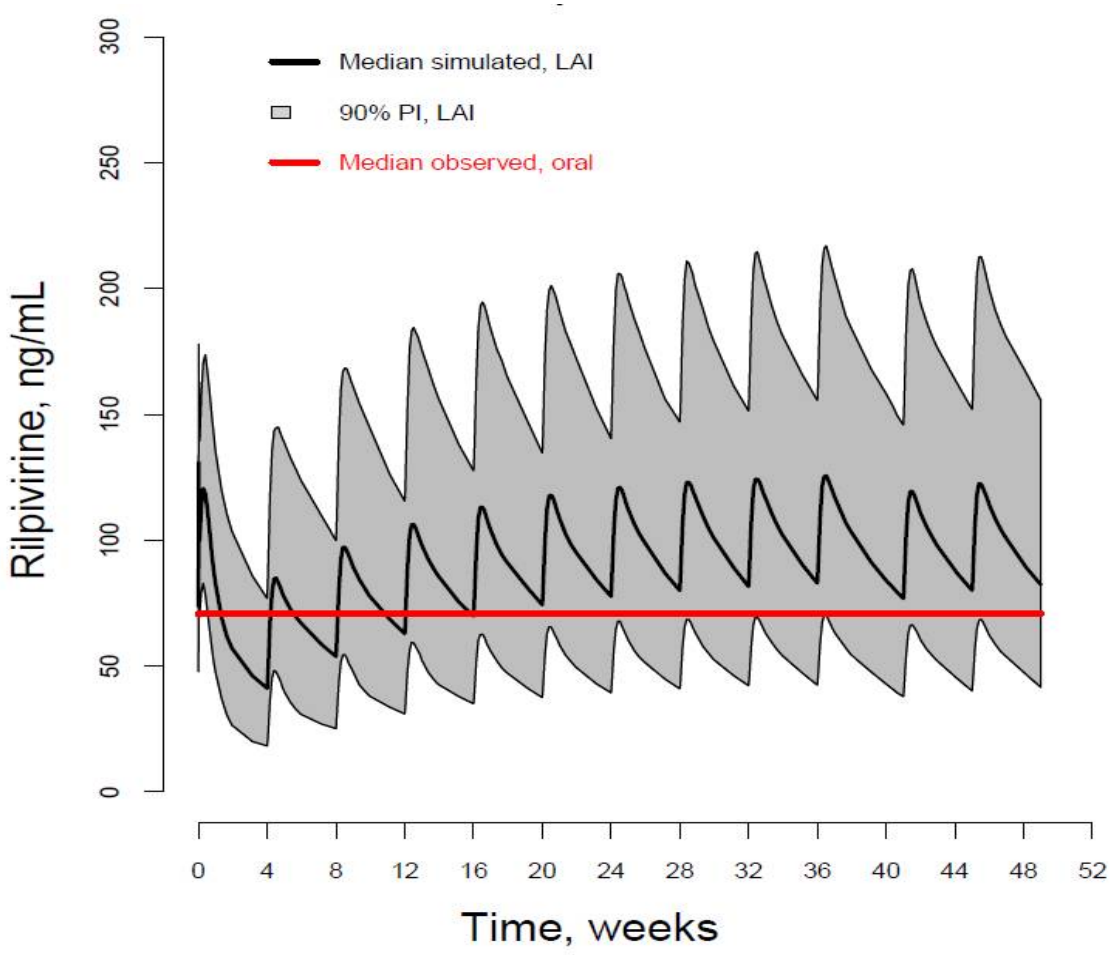
Figure 13 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q4W regimen (900 mg IM Day 1, then 600 mg IM Q4W thereafter^)



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)
Horizontal line at 72 ng/mL corresponds to median Cτ following oral RPV 25mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV Cτ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

At steady-state, a one week delay in dosing for the Q4W regimen is predicted to result in a median steady-state Cτ that remains above the median trough for RPV 25 mg (Figure 14). This supports allowance of some flexibility in the dosing regimen.

Figure 14 Impact of 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) RPV Plasma Concentrations versus Time for Optimized RPV LA Q4W dosing regimen (900 mg IM Day 1 and then 600 mg IM Q4W thereafter^)



*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 100 study visit); Week 4 = second injections (Week 104 study visit)

Horizontal line at 72 ng/mL corresponds to median Cτ following oral RPV 25 mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV Cτ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

Section 1. 11 Benefit: Risk Assessment

Revised to (changes struck through and underlined):

Section 1.11.1 Risk AssessmentSection

1.11.1.1 ~~GSK744~~ CAB and ~~GSK744~~ CAB LA

Since ~~GSK744~~ CAB is at an early stage of clinical development, and exposure in humans with or without HIV infection is limited, the clinical safety profile in humans has yet to be fully elucidated. The following risks have primarily been identified during routine

preclinical testing and/or in the clinical trial experience to date and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about the clinical experience to date and possible risks associated with treatment using CAB can be found in the Summary of Data and Guidance for the Investigator section of the IB.

Elevated Liver Transaminases

~~Two out of 183 subjects in the Induction Phase of ongoing study LAI116482 involving treatment naïve HIV patients receiving GSK744 have developed elevated liver enzymes, considered probably related to GSK744. Both subjects met protocol defined liver stopping criteria and stopped taking GSK744 as a result of these elevations. Transaminases returned to pre-treatment levels after stopping drug in both cases. In the two subjects, the peak ALT elevation was >10xULN and occurred approximately 4 weeks and 8 weeks, respectively, after initiating daily GSK744 60 mg+ ABC/3TC. In both cases the ALT and AST values were elevated while other liver tests remained normal (bilirubin, alkaline phosphatase, albumin). Neither subject developed clinical symptoms of liver dysfunction. No other subjects have required discontinuation of GSK744 as a result of a transaminase elevation. To date approximately 134 healthy volunteers have received 100 to 800 mg of GSK744 LA administered as a SC or IM injection. There have been no Grade 3 or Grade 4 ALT elevations while on GSK744 LA. There has been a single subject with a transient Grade 2 ALT elevation following the three monthly injections with GSK744 LA 400 mg that resolved while remaining on GSK744 LA.~~ A small proportion of participants in the CAB program to date (total exposure approximately 1198 to 01 April 2016) have developed transaminitis (elevated liver transaminases characterised by predominant ALT elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection and whilst a small number of others did not have alternative explanations, suggesting a mild form of DILI (drug induced liver injury) without hepatic dysfunction which resolved upon withdrawal of treatment with CAB.

Of the five participants with possible or probable cases of DILI identified in Phase 2 studies, four participants were receiving oral CAB and one participant developed probable DILI following CAB LA or Placebo LA administration.

Creatine Phosphokinase (CPK) elevations

Occurrences of asymptomatic, transient instances of elevations of CPK levels have been observed in Phase I studies and an ongoing Phase IIb ~~study~~ studies with ~~GSK744~~ CAB at dose levels of 10, 30 and 60 mg (LAI116482) and with CAB LA (200056). These generally appeared to be related to physical activity, were not associated with clinical symptoms and returned to pre-treatment levels in all cases. No subject has required a discontinuation of ~~GSK744~~ CAB as a result of a CPK elevation. Rhabdomyolysis of uncertain cause has been included in labeling for a currently available integrase inhibitor (raltegravir) but has not been seen in any subject receiving ~~GSK744~~ CAB to date.

Injection Site Reactions

The occurrence of ISRs was identified in rats and monkeys at all dose levels of ~~GSK744~~ CAB LA and associated with both the IM and SC route of administration. In humans, experience to date has demonstrated ISRs occur in the majority of exposed subjects but are generally mild (Grade 1) or moderate (Grade 2) and include tenderness, erythema, or nodule formation of several days duration. Reactions have been well tolerated and have ~~not to date been associated with~~ only rarely led to subject withdrawal.

Development of Resistance

Residual concentrations of ~~GSK744~~ CAB would remain in the systemic circulation of ~~subjects who stopped~~ participants for prolonged periods (up to 1 year) despite stopping treatment (e.g. for tolerability issues or treatment failure) ~~for prolonged periods (months)~~. ~~Subjects~~ Participants discontinuing ~~a~~ CAB LA regimen may be at risk for developing HIV-1 resistance to ~~GSK744~~ CAB many weeks after discontinuing injectable therapy.

Mitigation: Alternative oral HAART regimens will be ~~constructed for subjects stopping long acting therapy which~~ prescribed within four weeks after participants stop CAB LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus ~~minimization~~ minimizing of the risk of emergent resistance. The ~~Sponsor will continue to monitor subjects~~ participants in this study who discontinue ~~a~~ CAB LA ~~regimen~~ for any reason will be monitored for a minimum of 52 weeks from the time of the last CAB LA injection.

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that ~~GSK744~~ CAB LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of ~~GSK744~~ CAB LA. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Mitigation: Training will be provided to all sites on proper injection technique. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a PK sample, post dose ECG, vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the Medical Monitor notified. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of ~~GSK744~~ CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of ~~GSK744~~ CAB and ~~TMC278~~ RPV concentrations.

~~Section 1.10.1.2 TMC278~~

1.11.1.2. RPV and RPV LA

For safety and risk mitigation for ~~TMC278~~ RPV refer to the ~~RPV~~ rilpivirine prescribing information [Edurant Product Information, 20145].

~~1.10.1.3 TMC278 LA~~

~~Since TMC278 LA is at an early stage of clinical development, and exposure in humans with or without HIV infection is limited,~~ Information about the clinical ~~safety profile in humans~~ experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB. Beyond what has ~~yet to be fully elucidated~~ already been identified with oral RPV, no new systemic adverse reactions to RPV LA (same active moiety) have been observed. The following risks ~~have primarily been identified during routine preclinical testing and/or in the clinical trial experience to date and~~ are considered to be of ~~potential~~ specific clinical relevance ~~to clinical usage~~ in the context of ~~this protocol~~ IM use:

Inadvertent Intravenous Injection (Accidental Maladministration)

As with any intramuscular injection, it is possible that ~~TMC278~~ RPV LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of ~~TMC278~~ RPV LA. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with RPV LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Mitigation: Training will be provided to all sites on proper injection technique. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a PK sample, post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the Medical Monitor notified. Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints (Day 1, Week 32 and Week 48) for determination of ~~TMC278~~ RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of ~~GSK744~~ CAB and ~~TMC278~~ RPV concentrations.

~~1.10.1.6~~. 1.11.1.5 Risk of Treatment Failure

This study employs an induction / maintenance approach to the treatment of HIV-1 infection. Following virologic suppression, subjects will be transitioned off of a 3 drug ART regimen to a 2 drug ART regimen. ~~Although both~~ ~~GSK744~~ CAB and ~~TMC278~~ RPV have demonstrated antiviral activity in ~~large clinical~~ the Phase 2b studies ~~and the~~

LAI116482 (oral two drug ~~combination has demonstrated antiviral activity in study LAI116482, the risk of virologic failure in study~~ treatment) and 200056 ~~is unknown.~~ (through 48 weeks LA treatment). Viral loads will be closely monitored throughout the study.

Doses of the ~~GSK744~~ CAB LA and ~~TMC278~~ RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral formulations. Neither ~~GSK744~~ CAB LA or ~~TMC278~~ nor RPV LA, at any dose, has been used in HIV-1 infected subjects. Plasma samples will be collected throughout the Maintenance Period for determination of ~~GSK744~~ CAB and ~~TMC278~~ RPV concentration and possible pharmacokinetic correlation with virologic response.

Due to administration error, it is possible that a subject could receive an inadequate dose of ~~GSK744~~ CAB LA or ~~TMC278~~ RPV LA. Sub-therapeutic concentrations of either ~~GSK744~~ CAB LA or ~~TMC278~~ RPV LA could lead to virologic failure and possibly the development of resistance. HIV-1 RNA viral loads will be closely monitored throughout the injection period of the study.

Mitigation: HIV-1 RNA will be closely monitored throughout the study. Plasma samples will be collected throughout the Maintenance Phase for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response.

Section 1.11.2. Other Clinically Relevant Information

New Section added (underlined):

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochure. Please refer to Section 6: 'Summary of Data and Guidance for the Investigator'

Adverse Events of Special Interest:

Seizure:

Four cases of possible or definitive seizures have occurred in the CAB program cumulatively through 7 June 2016. Two of the cases occurred in HIV uninfected subjects with a prior history of seizure. Two cases occurred in HIV infected subjects, one case involved a subject in this study, 200056, and another case in the LAI116482 study, both cases displayed circumstantial and anecdotal evidence of illicit drug use which may have contributed to the event, and each case was determined by the Sponsor to not be reasonably likely related to CAB or RPV. Overall, there is insufficient evidence that CAB exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. However, seizure and seizure-like events will be closely monitored in clinical studies, including this study (200056). Any case of seizure or possible seizure must be reported to the Sponsor within 24 hours of notification, as detailed in Section 6.10.14.

Section 1.11.3 Benefit Assessment

Added line to section (underlined):

... Efficacy of the two-drug regimen, as oral agents, has been demonstrated through Week 96 of the ongoing LAI116482 study. Efficacy of the two-drug regimen, as LA agents, has been demonstrated through Week 48 of the ongoing 200056 study.

Section 2 Objectives and Endpoints

Added the Exploratory Objectives and Endpoints to table (underlined)

Objective	Endpoint
Primary	
To select an intramuscular dosing regimen of CAB LA plus RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg plus ABC/3TC orally once daily.	The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 based on intent to treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm. Proportion of subjects with protocol defined virologic failures over time
	Incidence and severity of AEs and laboratory abnormalities over time.
Secondary	
To evaluate the antiviral activity, tolerability, and safety of CAB 30 mg plus ABC/3TC orally once daily through the Induction and Maintenance Periods.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Absolute values and change from Baseline in plasma HIV-1 RNA. Absolute values and changes from Baseline in CD4+ cell counts. Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.
To evaluate the efficacy, tolerability, and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks, relative to CAB 30 mg plus ABC/3TC orally once daily, through Week 96 of the Maintenance Period.	Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time. Proportion of subjects with protocol defined virologic failures over time.
	Absolute values and change from Baseline in plasma HIV-1 RNA.
	Absolute values and changes from Baseline in CD4+ cell counts.
	Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death.
	Incidence and severity of AEs and laboratory abnormalities over time.

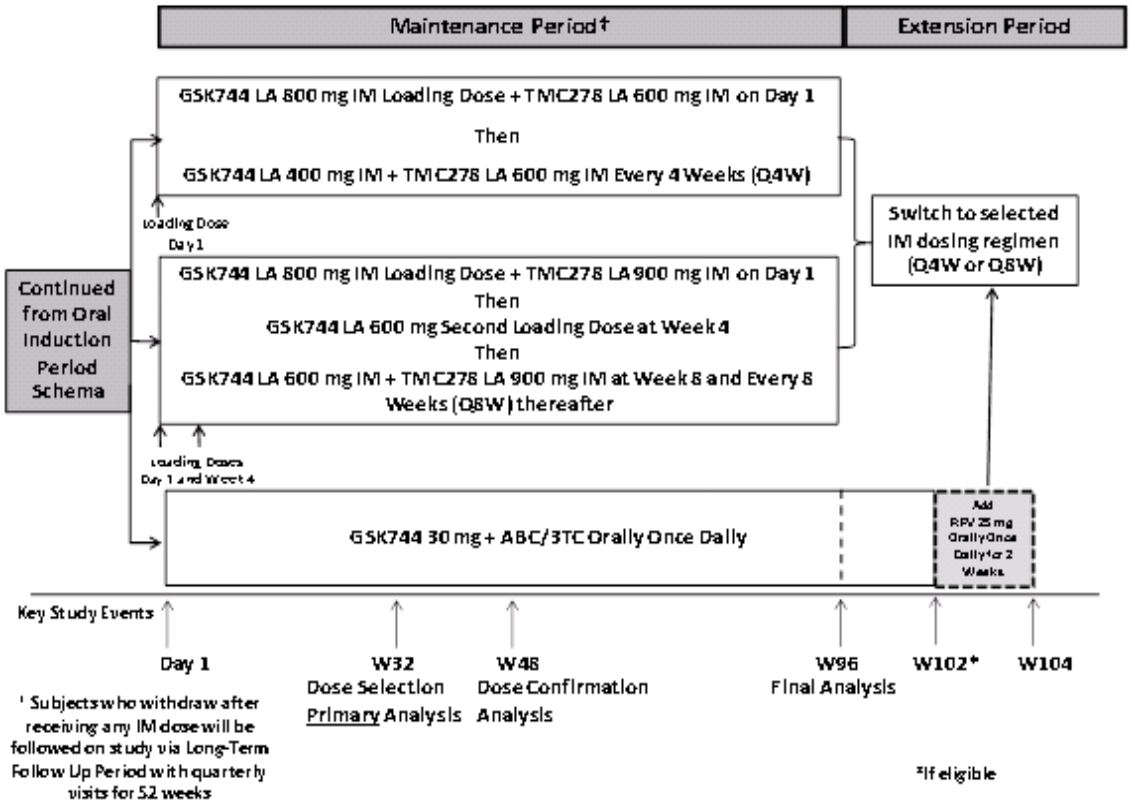
Objective	Endpoint
	Absolute values and changes in laboratory parameters over time.
To characterize CAB LA and RPV LA PK and to explore PK-PD relationships.	Plasma PK parameters for CAB LA and RPV LA (C_{trough} and concentrations post dose [~Cmax]) during the Maintenance Period. Plasma CAB and RPV trough concentrations will be used to determine when steady state is achieved for each CAB LA and RPV LA regimen. Relationship between plasma PK parameters and plasma HIV-1 RNA, CD4+ cell counts and/or occurrence of adverse events [AEs] through Week 48 of the Maintenance Period will be explored.
To assess the development of viral resistance in subjects experiencing protocol defined virologic failure.	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART.
To explore the effect of various demographic Baseline characteristics and adherence on virologic response of CAB and RPV over time.	Proportion of subjects with plasma HIV-1 RNA <50 c/mL over time.
To evaluate the treatment satisfaction for subjects on the long-acting injectable regimens with those on the oral regimen through Week 96 of the Maintenance Period.	Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time.
To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 32 of the Maintenance Period.	Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time.
To evaluate medication adherence over time.	Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.
Exploratory	
To evaluate the efficacy, tolerability, and safety of optimized IM dosing regimens CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Weeks 128 and 152 for subjects switching from the oral regimen therapy at the end of the Maintenace Period. To evaluate the long term efficacy, tolerability, and safety of IM dosing regimens CAB LA 400	Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 128 and 152 (Missing, Switch or Discontinuation = Failure, Extension Switch population) Proportion of subjects with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 128 and 152 using the FDA Snapshot algorithm (Extension Switch population)

Objective	Endpoint
mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Week 152 for subjects who continued randomized IM dosing in the Extension Period.	Proportion of subjects with protocol defined virologic failures over time Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.Absolute values and changes in CD4+ cell counts over time Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.

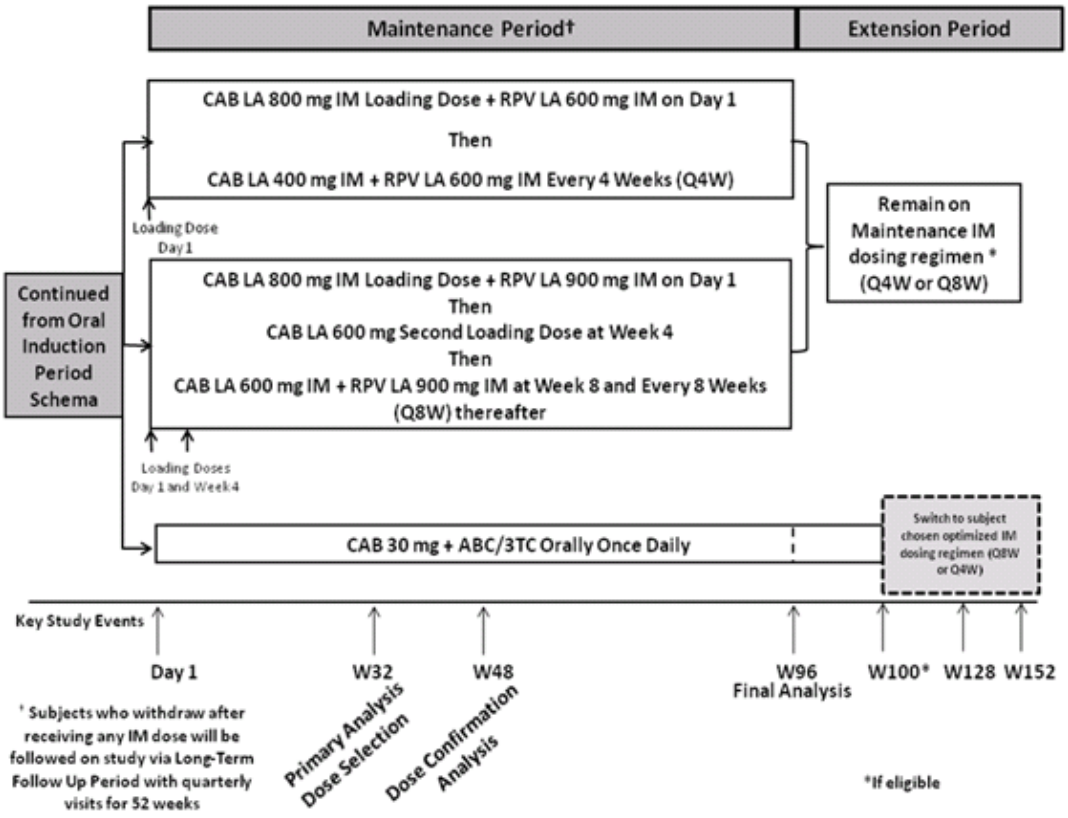
Section 3.1 Study Design Schematic

Updated the Extension Period of schematic:

Old:



New:



Section 3.2.5 Extension Period

Redesign of the Extension Period (Old version, strikethrough; New version, underlined):

Old:

~~A single IM dosing regimen will be selected as according to the RAP to be evaluated in the Extension period.~~

~~Section 3.2.5.1 Entering From the GSK744 LA + TMC278 LA Arm~~

~~All subjects who successfully complete 96 weeks of GSK744 LA + TMC278 LA treatment in the Maintenance Period will continue to have access to both GSK744 LA and TMC278 LA in the Extension Period until study treatment is either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated.~~

~~Subjects will be switched to the selected dose at Week 96 and will continue to receive the selected IM dosing regimen for the remainder of study participation. Safety and efficacy assessments will be conducted every 16 weeks after the initial switch. Dosing visits will~~

~~occur according to the selected dosing regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.~~

~~Section 3.2.5.2 Entering From the GSK744 + ABC/3TC Arm~~

~~All subjects who successfully complete 96 weeks of GSK744 + ABC/3TC treatment in the Maintenance Period will have the option to either continue study participation by switching to GSK744 LA + TMC278 LA in the Extension Period, or to complete their study participation at Week 96 (no withdraw visit needed).~~

~~Subjects who choose to continue on to the Extension Period will need to be assessed for eligibility to begin the selected GSK744 LA + TMC278 LA regimen. Subjects will continue on their Maintenance regimen (GSK744 + ABC/3TC) while eligibility is being confirmed. The Week 100 HIV-1 RNA result will be used to determine eligibility and subjects will have a visit at approximately (depending on availability of results) Week 102 to assess eligibility. All subjects with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 100 visit are eligible to enter the Extension Period. Note: Subjects with an HIV-1 RNA ≥ 50 c/mL result from the Week 100 visit may be allowed to enter the Extension Period only at the discretion of the medical monitor or withdrawn.~~

~~Subjects eligible to enter the Extension Period will add a short course (2 weeks) of RPV 25 mg orally once daily to their GSK744 + ABC/3TC regimen at Week 102 before initiating dosing with the long acting regimen at Week 104. This allows subjects to achieve steady state of RPV prior to beginning the long acting regimen.~~

~~At Week 104, subjects will receive their last dose of GSK744 + ABC/3TC + RPV in the clinic~~ and ~~will begin dosing with the selected IM regimen. These subjects will receive loading doses as per the requirement of the selected regimen (see Section 5.1.6 for dosing regimens).~~

~~Subjects will continue study treatment until GSK744 LA and TMC278 LA are either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either GSK744 LA or TMC278 LA is terminated. Safety and efficacy assessments will be conducted every 16 weeks after the initial switch. Dosing will occur according to the selected regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.~~

~~Subjects not eligible to enter the Extension Period will end their study participation (Week 102 will be the last study visit, no withdraw visit needed). Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.~~

New:

Both IM dosing regimens (Q8W and Q4W) will continue evaluation in the Extension period. Subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option of continuing study

participation by switching to an optimized IM dosing regimen of their choice (either Q8W or Q4W).

Section 3.2.5.1 Entering From the CAB LA + RPV LA Arm

All subjects who successfully complete 96 weeks of CAB LA + RPV LA treatment in the Maintenance Period will continue with their current IM dosing regimen of CAB LA and RPV LA in the Extension Period until:

- study treatment is locally approved and commercially available,
- the subject no longer derives clinical benefit,
- the subject meets a protocol-defined reason for discontinuation
- the development of either CAB LA or RPV LA is terminated.

Subjects will remain on their current regimen after Week 96 and will continue to receive their Maintenance Period IM dosing regimen for the remainder of study participation. Safety and efficacy assessments will be conducted every 16 weeks. Dosing visits will occur according to the selected dosing regimen. See the Time and Events Schedule Section 6.5 and Section 6.6 for more information.

Section 3.2.5.2 Eligibility for the Extension Period for Subjects Entering From the CAB 30 mg + ABC/3TC Arm

All subjects with an undetectable HIV-1 RNA (<50 c/mL) at the Week 96 visit are eligible to enter the Extension Period. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week 96 are not eligible to enter the Extension Period and will not be allowed a repeat to determine eligibility.

Result of HIV-1 RNA at Week 96	**Action**
<50 c/mL	Begin Extension Period
≥50 c/mL but <400 c/mL	Single repeat allowed only after consultation and approval from medical monitor
Single repeat <50 c/mL	Begin Extension Period
Single repeat ≥50 c/mL	Cannot begin Extension Period and must be withdrawn from study; Complete withdrawal visit.
≥400 c/mL	Cannot begin Extension Period and must be withdrawn from study; Complete withdrawal visit.

Should a subject be allowed a repeat, results of this repeat must be available prior to next visit, therefore the time needed for scheduling the visit, lab draws and lab analysis should be considered.

In addition to the viral load criteria above, if in the opinion of the Investigator, a subject experiences a significant safety event while taking either CAB or RPV, Extension eligibility will be determined ONLY in consultation with the medical monitor.

Subjects ineligible for the Extension Period will be withdrawn.

If the subject is ineligible for the Extension Period, samples will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

Section 3.2.5.3 Entering From the CAB 30 mg + ABC/3TC Arm

All subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option to continue study participation by switching to the optimized IM dosing regimen of their choice (either Q8W or Q4W) of CAB LA + RPV LA in the Extension Period. Subjects not choosing to switch to an optimized long acting regimen will complete their study participation at Week 96.

Subjects who choose to continue on to the Extension Period will be assessed for eligibility to begin their selected CAB LA + RPV LA regimen as described in Section 3.2.5.2. Subjects will continue on their oral Maintenance regimen (CAB 30 mg + ABC/3TC) until Week 100 while eligibility is being confirmed.

In order to qualify to receive CAB LA + RPV LA injections at Week 100, the HIV-1 RNA results from the Week 96 visit must be undetectable (<50 c/mL; a single repeat HIV-1 RNA test may be allowed prior to Week 100 following consultation with the Medical Monitor).

If the Optimized Q4W IM Dosing Regimen is Selected by the Subject

At visit Week 100, participants will return to the clinic, take the last dose of their oral regimen (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104 and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104, but not later than Week 104, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 injection, the interval between injection visits should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if

the length of time between injections exceeds, or is projected to exceed, 5 weeks from the previous injection.

If the Optimized Q8W IM Dosing Regimen is Selected by the Subject

At visit Week 100, subjects will return to the clinic, take the last dose of their oral (CAB 30 mg + ABC/3TC), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second loading injections will be administered at Week 104 (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 8 weeks thereafter. The dosing window for the second injection allows administration between Week 103 and Week 104, but preferably not later than Week 104. Starting at the Week 112 injection, the interval between injection visits should be limited to a maximum of 9 weeks. If the length of time between injections exceeds, or is projected to exceed 9 weeks, the Medical Monitor must be contacted to discuss individual subject case management. After Week 112, a dosing window (±7 days) for injections is allowed, but not preferred.

Subjects will continue study treatment until:

- study treatment is locally approved and commercially available,
- the subject no longer derives clinical benefit,
- the subject meets a protocol-defined reason for discontinuation
- the development of either CAB LA or RPV LA is terminated..

Safety and efficacy assessments will be conducted as per the Time and Events schedule (Section 6.5 and Section 6.6 for more information). Dosing will occur according to the selected regimen.

Subjects not eligible to enter the Extension Period will end their study participation. Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

If one of the optimized IM dosing regimens (Q8W or Q4W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who selected a discontinued optimized IM dosing regimen may be given the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

Section 3.2.8 Independent Data Monitoring Committee

Updated section to reflect new IDMC monitoring for Extension Period

... If one of the IM dosing regimens (Q4~~8~~W or Q~~8~~4W) is discontinued as a result of an IDMC review or any subsequent analysis, those subjects who have not met any clinical management criteria for discontinuation and who were randomized to the discontinued dosing regimen , or selected a discontinued optimized IM dosing regimen, may be given

the option to discontinue permanently from the study or to continue on the remaining IM dosing regimen at the next scheduled visit.

As subjects enter the Maintenance Period of the study, if the number of protocol defined virologic failures meets or exceeds the pre-specified thresholds specified in the IDMC Charter, this will be considered strong evidence of an inadequate response and will trigger a comprehensive data review by the IDMC. Similar thresholds will be used by the IDMC to monitor the number of protocol defined virologic failures for subjects switching from oral CAB 30 mg + ABC/3TC to an optimized IM dosing regimen during the Extension Period. The IDMC charter will contain details of this continual monitoring of the protocol defined virologic failure rates, the specifics around what will trigger a data review, and the safety summaries and efficacy analyses that will be provided should a data review be required.

Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

Section 3.3 Discussion of Design

Added the following wording (underlined):

The Extension Period will allow participants on the oral Maintenance Period regimen who successfully complete Week 96 with an HIV-1 RNA viral load <50 c/mL the opportunity to choose an optimized IM dosing regimen (Q8W or Q4W). This will permit an evaluation of the ability of the optimized investigational two-drug long acting combinations (see Section 5.1.6) to maintain virologic suppression over time. This period will also allow participants currently on a IM Maintenance Period regimen who successfully complete Week 96 with an HIV-1 RNA viral load <50 c/mL the ability to continue to receive their current IM dosing regimen and to generate additional long-term safety and efficacy data for randomized IM dosing regimens.

A planned Week 128 analysis will primarly evaluate the efficacy, tolerability, and safety of the optimized IM dosing regimens through 28 weeks of optimized IM treatment in subjects switching from oral Maintenance therapy. Long term durability of virologic suppression of the randomized long-acting two-drug regimens through Week 128 may also be evaluated.

A Week 152 analysis will permit an evaluation of the ability of the randomized and optimized investigational two-drug long-acting combinations to showcase long-term durability of virologic suppression. Additional long-term safety and efficacy data for all IM dosing regimens will be generated.

Section 4.5 Withdrawal Criteria

Removed the following Withdrawal Criteria (strikethrough):

- ~~Change from Baseline: Increase in QTc > 60 msec~~

Section 5.1.6 Dosage and Administration

Updated Extension Period Dosing

Old:

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injections (No TMC278 LA)
Week 8 to Week 88 (2 injections every 8 weeks)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
Week 4 to Week 92 (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection

GSK744 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
If continuing to Extension Period:	
Week 96 to Week 102 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily
If eligible to enter Extension Period:	
Week 102 to Week 104 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X GSK744 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal
Extension Period (Week 96 plus+)	
If GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks is selected:	
Week 96 plus+ (2 injections every 8 weeks)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
If switching from Oral Arm:	
Week 104 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
Extension Period (Week 96 plus+)	
If GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks is selected:	
Week 108 – 2nd loading dose (1 injection once)	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injections (No TMC278 LA)
Week 112 plus+	Receive GSK744 LA 600 mg given as 1 X 3 mL IM injection

(2 injections every 8 weeks)	Receive TMC278 LA 900 mg given as 1 X 3 mL IM injection
If GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks is selected:	
Week 96 plus+ (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm:	
Week 104 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive GSK744 LA 800 mg given as 2 X 2 mL IM injections Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection
Week 108 plus+ (2 injections every 4 weeks)	Receive GSK744 LA 400 mg given as 1 X 2 mL IM injection Receive TMC278 LA 600 mg given as 1 X 2 mL IM injection

*Or through Week 104 if eligible to enter the Extension Period.
+until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of GSK744 or TMC278 is terminated

New (Modifications Underlined):

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections

	Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections (No RPV LA)
Week 8 to Week 88 (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 4 to Week 92 (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
CAB 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
If continuing to Extension Period:	
Week 96 to Week 100 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Extension Period (Week 96 +)	
If subject was randomized to the Q8W regimen during the Maintenance Period:	
Week 96 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
If switching from Oral Arm and the Optimized Q8W regimen is selected by subject:	
Week 100 – 1st loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose	Receive CAB LA 600 mg given as 1 X 3 mL IM injections

(2 injection once)	Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 112 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
If Subject was Randomized to the Q4W regimen during the Maintenance Period:	
Week 96 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm and the Optimized Q4W regimen is selected by subject:	
Week 100 – 1st loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose (2 injections once)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 108 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection

*Or through Week 100 if eligible to enter the Extension Period.
+until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of CAB or RPV is terminated

Section 5.9.2 Prohibited Medications and Non-Drug Therapies

Modified the following line (removed items, strikethrough; added items underlined):

Hepatitis C infection ~~treatment will not be permitted~~ therapy is allowed during the study, but interferon-based HCV therapy is prohibited throughout the entire study. Options for treatment of hepatitis C must be discussed with the Medical Monitor prior to initiation of therapy.

Section 6.2 Time and Events Table – Maintenance Period for IM Regimen (CAB LA + RPV LA Q8W)

Removed footnote 'o' and modified footnote 'n'

n) Subjects will continue to receive ~~the selected Extension~~ their Maintenance Period dosing regimen in the Extension Period (~~either~~ Q8W ~~or Q4W~~) at this visit. ~~If~~

~~switching to Q4W, injections are 1 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. Subjects may immediately begin the new regimen at Week 96.~~

o) ~~Remind subjects of the potential change in study treatment and visit frequency beginning at Week 96~~

Section 6.3 Time and Events Table – Maintenance Period for IM Regimen (CAB LA + RPV LA Q4W)

Removed footnote 'o' and modified footnote 'n'

n) Subjects will <u>continue to</u> receive ~~the selected Extension~~ <u>their Maintenance Period</u> dosing regimen in the <u>Extension Period</u> (~~either~~ Q4W ~~or Q4W~~) at this visit. ~~If switching to Q4W, no loading dose is necessary injections are 1 x GSK744 LA 600 mg IM + 1 x TMC278 LA 900 mg IM.~~

o) ~~Remind subjects of the potential change in study treatment and visit frequency beginning at Week 96~~

Section 6.4 Time and Events Table – Maintenance Period for Oral Regimen (CAB 30 mg + ABC/3TC)

Modified T&E table and footnotes. Removed Weeks 100, 102 and 104 from table:

Old:

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
Verify Eligibility	X																								X [l]		X [l, n]		
Randomization	X																												
Symptom Directed PE & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X				X		X				X		X		X		X		X		X		X	X	X	X	X
Weight and BMI	X								X				X												X			X	X
ECG [d]	X pre	X	X				X		X				X				X				X				X			X pre	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Diary (D)ispensation and (R)eview [e]	R							D	R			D	R																
eC-SSRS [f]	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X				X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
HIVTSQ(s) [g]	X pre		X						X				X												X				X
HIVTSQ(c) [g]									X																				X
HIVMQ [g]			X						X				X												X				X [g]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X	X
Pregnancy Test (S)erum/(U)rine	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S		S		S		S		S	S	S	U	S
HIV-1 RNA & sample for storage [i]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X [n]	X	X	X
CD4+	X	X	X				X		X				X		X				X		X				X		X	X	X
CD8+	X								X				X												X				
Urinalysis	X								X				X						X						X			X	X
Fasting: Glucose, Insulin, Cholesterol (Total, HDL and LDL) and Triglycerides [j]	X	X							X				X						X						X			X	X
PT/PTT/INR	X								X				X												X			X	X
PK Sample [k]	X								X				X												S			S	X
Study Treatment Dispensation and Accountability [o]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X [m]	X	X Add RPV	X Add injection	
Visit Reminder	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [p]	X [m,p]	X [p]	X [p]	X [p]	X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100[m]	W 102[m]	W 104[m]	WD [q]
Contact																													
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	X	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index
Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including compliance.

a. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.
b. Measure vital signs after about 5 minutes of rest in a semi-supine position.
c. BMI collected at Week 104 only.
d. 12-Lead ECG – Conduct pre-dose at Day 1 and Week 104. At all other visits, it is preferable to conduct 2 – 4 hours after dosing.
e. Review PK diary at the beginning of the visit to verify time of last dose. PK samples must be collected within the window of 20-28 hours after the last dose taken. Contact the study team for guidance in cases when subject's last dose is not within window. Visit may need to be rescheduled.
f. Preferably completed at the beginning of the visit.
g. Conduct the HIVTSQ(s) at Day 1 prior to dosing and post dosing where possible at all other visits. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ preferably at the beginning of the visit, but may be completed at any time during the visit.
h. Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
i. Plasma for storage samples are collected for possible future analyses, as back- up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures
j. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
k. All PK samples should be taken pre-dose within 20-28 hours after the last dose of IP taken. Subjects will take their dose of IP in the clinic at PK visits. S=Storage
l. Assess subject's willingness to continue on to the Extension Period. If not continuing into the Extension Period, this is the subject's last study visit.
m. For subjects continuing into the Extension Period only.
n. The Week 100 HIV-1 RNA result must be <50 c/mL to be eligible to continue into the Extension Period. See Section 3.2.5.3. Subjects ineligible for Extension will end their study participation at Week 102 (no withdrawal visit needed).
o. Subjects will discontinue RPV at Day 1 and begin taking 1 x GSK744 + 1 x ABC/3TC tablet once daily. At Week 96 and Week 100, while awaiting eligibility for Extension, subjects will continue their GSK744+ABC/3TC regimen. At Week 102, subjects eligible to enter the Extension Period will add once daily RPV to their GSK744+ABC/3TC regimen and continue to take GSK744+ABC/3TC +RPV once daily through Week 104. At Week 104, subjects will take final dose of GSK744+ABC/3TC+RPV in the clinic and begin the selected IM regimen (Q8W or Q4W). See Section 5.1.6 for IM dosing administration as loading doses are required.
p. Remind subjects of the change in study and assessments for eligibility into Extension.
q. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.

New:

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Verify Eligibility	X																								X [k]	
Randomization	X																									
Symptom Directed PE & Medical Assessment [a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X and smoking status
Vital Signs (BP, HR) [b]	X	X	X				X		X				X		X		X		X		X		X		X	X
Weight and BMI [c]	X								X				X												X	X
ECG [c]	X pre	X	X				X		X				X				X				X				X	X
HIV Associated Conditions, AE and SAE Assessment, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Diary (D)ispensation and (R)eview [d]	R							D	R			D	R												D	
eC-SSRS [e]	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X	X

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
HIVTSQ(s) [f]	X pre		X						X				X												X	X
HIVTSQ(c) [f]									X																	X
HIVMQ [f]			X						X				X												X	X [f]
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X
Pregnancy Test (S)erum/(U)rine [g]	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S		S		S		S		S	S
HIV-1 RNA & sample for storage [h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X [m]	X
CD4+	X	X	X				X		X				X		X				X		X				X	X
CD8+	X								X				X												X	
Urinalysis	X								X				X						X						X	X
Fasting: Glucose, Insulin, Cholesterol (Total, HDL and LDL) and Triglycerides [i]	X	X							X				X						X						X	X
PT/PTT/INR	X								X				X												X	X
PK Sample [j]	X								X				X												S	X
Study Treatment Dispensation and Accountability [n]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X [q]	
Study Treatment																										

Procedures For Maintenance – **ORAL** regimen	D1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	WD [p]
Administration																										
Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X[l,o]	X
Subject Contact Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X

D=Day W=Week Pre=Pre-dosing PE = Physical Exam BMI=Body Mass Index

Gray shading indicates telephone safety assessments that will include interviewing the subject for adverse events, concomitant medications, HIV associated conditions and any other issues including compliance.

a. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management and/or care of the subject.
b. Measure vital signs after about 5 minutes of rest in a semi-supine position.
c. 12-Lead ECG – Conduct pre-dose at Day 1. At all other visits, it is preferable to conduct 2 – 4 hours after dosing.
d. Review PK diary at the beginning of the visit to verify time of last dose. PK samples must be collected within the window of 20-28 hours after the last dose taken. Contact the study team for guidance in cases when subject's last dose is not within window. Visit may need to be rescheduled.
e. Preferably completed at the beginning of the visit.
f. Conduct the HIVTSQ(s) at Day 1 prior to dosing and post dosing where possible at all other visits. Conduct the HIVTSQ(c, WD) at WD ONLY if the subject WD between Week 8 and Week 32. Conduct the HIVMQ preferably at the beginning of the visit, but may be completed at any time during the visit.
g. Women of childbearing potential only. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A positive urine test should be confirmed with a stat serum test. If positive, subject will need to be WD.
h. Plasma for storage samples are collected for possible future analyses, as back- up in case of lost or damaged in transit to the lab and for geno/pheno analyses for virologic failures
i. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
j. All PK samples should be taken pre-dose within 20-28 hours after the last dose of IP taken. Subjects will take their dose of IP in the clinic at PK visits. S=Storage
k. Assess subject's willingness to continue on to the Extension Period. If not continuing into the Extension Period, this is the subject's last study visit.
l. For subjects continuing into the Extension Period only.
m. The Week 96 HIV-1 RNA result (or single re-test prior to Week 100) must be <50 c/mL to be eligible to continue into the Extension Period. See Section 3.2.5.2. Subjects ineligible for Extension will end their study participation at Week 96 (withdrawal visit needed).
n. Subjects will discontinue RPV at Day 1 and begin taking 1 x CAB 30 mg + 1 x ABC/3TC tablet once daily. At Week 96, while awaiting eligibility for Extension, subjects will continue their CAB 30 mg+ABC/3TC regimen.
o. Remind subjects of the change in study and assessments for eligibility into Extension.
p. Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
q. Assess Treatment Accountability only

Section 6.5 Time and Events Table – Extension Period for IM Regimen (CAB LA+ RPV LA-Q8W

Old:

Procedures for Extension if Q8W is Selected	W 104 [a]	~~W 108[b] From Oral Arm Only~~	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [c]	W 200 [c]	WD [n, o]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [d]	X	~~X~~	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "b" for continuation of visit schedule after Week 200. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [e]	X		X		X		X		X		X		X		X	~~a. Subjects switching from the oral regimen will complete Week 104 visit as per the Maintenance T&E Section 6.4.~~
Weight & BMI	X		X		X		X		X		X		X		X	~~b. Week 108 visit is only for subjects switching from the oral arm.~~
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	~~X~~	X	X	X	X	X	X	X	X	X	X	X	X	X	c. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 192, Week 216 will be conducted just like Week 200 and Week 224 will be conducted just like Week 192.
12-Lead ECG [f]	X	~~X~~	X		X		X		X		X		X		X	d. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
Clinical Chemistry and Hematology	X	~~X~~	X		X		X		X		X		X		X	e. Measure vital signs after about 5 minutes of rest in a semi-supine position.
Pregnancy Testing	U	~~U~~	U	U	U	U	U	U	U	U	U	U	U	U	U	f. Can be done at any time during the visit. g. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test

Procedures for Extension if Q8W is Selected	W 104 [a]	~~W 108[b] From Oral Arm Only~~	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [c]	W 200 [c]	WD [n, o]	Notes
(U)rine [g]																should be confirmed with a stat serum test. If (+), subject will need to be WD.
HIV-1 RNA and sample for storage [h]	X		X		X		X		X		X		X		X	h. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
CD4+	X		X		X		X		X		X		X		X	i. Fast overnight; minimum of a 6 hour fast is acceptable.
Urinalysis	X		X		X		X		X		X		X		X	j. Samples should be collected pre-dose.
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [i]	X		X		X		X		X		X		X		X	k. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.
PT/PTT/INR															X	l. Q8W Injections are 1 x GSK744 LA 600 mg IM + 1 x TMC278 LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
PK Sample (S)torage [j]	S		S		S		S		S		S		S		X	
ISR Diary Dispensation [k]	E	~~E~~	E	E	E	E	E	E	E	E	E	E	E	E	E review	
Study Treatment Administration [l]	X [a]	~~X [m]~~	X	X	X	X	X	X	X	X	X	X	X	X		m. Subjects switching from the oral arm will receive their 2nd loading dose injection of 1 x GSK744 LA 600 mg (no TMC278 LA).

Procedures for Extension if Q8W is Selected	W 104 [a]	~~W 108[b] From Oral Arm Only~~	W 112	W 120	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [c]	W 200 [c]	WD [n, o]	Notes
Subject Visit Reminder Contact	X	~~X~~	X	X	X	X	X	X	X	X	X	X	X	X		n. Or Long-Term Follow Up o. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.
Subject Contact Detail Confirmation	X	~~X~~	X	X	X	X	X	X	X	X	X	X	X	X		

New:

Added Visits W101 and W121 for subjects switching from oral to the Q8W IM regimen.

Added labs and procedures for subjects switching from oral to the Q8W IM regimen, denoted with footnote 'n'.

Removed the following footnotes:

~~p. Subjects switching from the oral regimen will complete Week 104 visit as per the Maintenance T&E Section 6.4.~~
~~q. Week 108 visit is only for subjects switching from the oral arm.~~
~~r. Samples should be collected pre-dose.~~
~~m. Subjects switching from the oral arm will receive their 2nd loading dose injection of 1 x GSK744 LA 600 mg (no TMC278 LA).~~

Added the following footnotes:

h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. A second Week 100 and 128 PK sample will be collected approximately 2 hours after the last injection

k. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q8W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required. (W100=1st loading dose; W104=2nd loading dose
n. Procedures and visits for subjects who switch from oral to the optimized Q8W IM dosing regimen.
o. First Extension Period visit for subjects continuing Q8W dosing from the Maintenance Period.

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "a" for continuation of visit schedule after Week 200. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [c]	X		X	X			X		X		X		X		X		X	a. Continue this pattern for visits for the remainder of the study. For example, Week 208 will be conducted just like Week 192, Week 216 will be conducted just like Week 200 and Week 224 will be conducted just like Week 192.
Weight & BMI	X		X	X			X		X		X		X		X		X	b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management.
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG [d]	X		X	X			X		X		X		X		X		X	c. Measure vital signs after about 5 minutes of rest in a semi-supine position.
Clinical Chemistry and Hematology	X	X	X	X	X [n]	X	X		X		X		X		X		X	d. Can be done at any time during the visit. e. A (-) urine pregnancy test is required prior to any injection and as required by medical

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
Pregnancy Testing (U)rine [e]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD.
HIV-1 RNA and sample for storage [f]	X		X	X	X [n]		X		X		X		X		X		X	f. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
CD4+	X		X	X	X [n]		X		X		X		X		X		X	g. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
Urinalysis	X		X	X	X [n]		X		X		X		X		X		X	h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. A second Week 100 and 128 PK sample will be collected approximately 2 hours after the last injection.
Fasting Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [g]	X		X	X	X [n]		X		X		X		X		X		X	i. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF.
PT/PTT/INR																	X	j. Q8W Injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls**
PK Diary (D)ispensation and (R)eview	R [n]																	
PK Sample (S)torage [h]	S	S	S	S	S [n]	S	S		S		S		S		S		X	
ISR Diary Dispensation [i]	E		E	E	E		E	E	E	E	E	E	E	E	E	E	E review	

Procedures for Extension - Q8W	W 100 [n]	W 101 [n]	W 104 [o]	W 112	W 120	W 121 [n]	W 128	W 136	W 144	W 152	W 160	W 168	W 176	W 184	W 192 [a]	W 200 [a]	WD [l, m]	Notes
Study Treatment Administration [j]	X [k]		X [k]	X	X		X	X	X	X	X	X	X	X	X	X		**(as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		k. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q8W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required. (W100=1st loading dose; W104=2nd loading dose)
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		l. Or Long-Term Follow Up m. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone. n. Procedures and visits for subjects who switch from oral to the optimized Q8W IM dosing regimen. o. First Extension Period visit for subjects continuing Q8W dosing from the Maintenance Period.

Section 6.6 Time and Events Table – Extension Period for IM Regimen (CAB LA + RPV LA – Q4W)

Old:

Procedures for Extension if Q4W is Selected	W 100 [a]	W 104 [a]	W 108	W 112	W 116	W 120	W 124	W 128 [b]	W 132 [b]	W 136 [b]	W 140 [b]	WD [l, m]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "b" for continuation of visit schedule after Week 140. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [d]	X		X				X				X	X	a. Subjects switching from the oral regimen will complete Week 100 and 104 visits as per the Maintenance T&E Section 6.4. b. Continue this pattern for visits for the remainder of the study. For example, Week 144 will be conducted just like Week 128, Week 148 will be conducted just like Week 132, Week 152 will be conducted just like Week 136 and Week 156 will be conducted just like Week 140. c. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject management. d. Measure vital signs after about 5 minutes of rest in a semi-supine position. e. Can be done at any time during the visit. f. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD. g. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and
Weight & BMI	X		X				X				X	X	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG [e]	X		X				X				X	X	
Clinical Chemistry and Hematology	X	X	X				X				X	X	
Pregnancy Testing (U)rine [f]	U	U	U	U	U	U	U	U	U	U	U	U	
HIV-1 RNA and sample for storage [g]	X	X	X				X				X	X	

Procedures for Extension if Q4W is Selected	W 100 [a]	W 104 [a]	W 108	W 112	W 116	W 120	W 124	W 128 [b]	W 132 [b]	W 136 [b]	W 140 [b]	WD [l, m]	Notes
CD4+	X	X	X				X				X	X	geno/pheno analyses for virologic failures. h. Fast overnight; minimum of a 6 hour fast is acceptable. i. Samples should be collected pre-dose. j. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. k. l. Q4W Injections are 1 x GSK744 LA 400 mg IM + 1 x TMC278 LA 600 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring TMC278 LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.** m. Or Long-Term Follow Up n. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.
Urinalysis	X		X				X				X	X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X		X				X				X	X	
PT/PTT/INR												X	
PK Sample (S)torage [i]	S	S	S				S				S	X	
ISR Diary Dispensation [j]	E	E	E	E	E	E	E	E	E	E	E	E review	
Study Treatment Administration [k]	X [a]	X [a]	X	X	X	X	X	X	X	X	X		
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X		
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X		

New:

Added Visits W101, W121 and W144 for subjects switching from oral to the Q4W IM regimen.

Added labs and procedures for subjects switching from oral to the Q4W IM regimen, denoted with footnote 'm'.

Removed the following footnotes:

~~a. Subjects switching from the oral regimen will complete Week 100 and 104 visits as per the Maintenance T&E Section 6.4.~~
~~h. Samples should be collected pre-dose.~~
~~i. Subjects switching from the oral arm will receive their 2nd loading dose injection of 1 x GSK744 LA 600 mg (no TMC278 LA).~~

Added the following footnotes:

h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. A second Week 100 and 128 PK sample will be collected approximately 2 hours after the last injection
n. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q4W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required.
m. Procedures and visits for subjects who switch from oral to the optimized Q4W IM dosing regimen.

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
Symptom Directed Physical Exam, ISR and Medical Assessment [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***See footnote "a" for continuation of visit schedule after Week 144. Continue until either locally approved and commercially available, the subject no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.***
Vital Signs (BP, HR) [c]	X		X [m]	X [m]	X					X				X	X	a. Continue this pattern for visits for the remainder of the study. For example, Week 148 will be conducted just like Week 132, Week 152 will be conducted just like Week 136, Week 156 will be conducted just like Week 140 and Week 160 will be conducted just like Week 144.
Weight & BMI	X		X		X					X				X	X	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG [d]	X		X [m]	X [m]	X					X				X	X	
Clinical Chemistry and Hematology	X	X	X	X	X	X [m]	X [m]	X	X [m]	X				X	X	
Pregnancy Testing (U)rine [e]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	
HIV-1 RNA and sample for storage [f]	X		X	X	X	X [m]	X [m]		X [m]	X				X	X	
CD4+	X		X	X	X	X [m]	X [m]		X [m]	X				X	X	
Urinalysis	X		X [m]	X [m]	X	X [m]	X [m]		X [m]	X				X	X	b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for subject
Fasting Glucose, Cholesterol (Total, HDL	X		X [m]	X [m]	X	X [m]	X [m]		X [m]	X				X	X	

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
and LDL) and Triglycerides [g]																management. c. Measure vital signs after about 5 minutes of rest in a semi-supine position. d. Can be done at any time during the visit. e. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), subject will need to be WD. f. Plasma for storage samples are collected for possible future analyses, back-up in
PT/PTT/INR															X	
PK Diary (D)ispensation and (R)eview	R [m]															
PK Sample (S)torage [h]	S	S	S	S	S	S [m]	S [m]	S	S [m]	S				S	X	
ISR Diary Dispensation[i]	E		E	E	E	E	E		E	E	E	E	E	E	E review	
Study Treatment Administration [j]	X [n]		X	X	X	X	X		X	X	X	X	X	X		
Subject Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
Subject Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		cases of loss/damage in transit and geno/pheno analyses for virologic failures. g. Fast overnight; however, a minimum of a 6 hour fast is acceptable. h. Take PK samples pre-dose except Week 101 and Week 121 which can be taken at any time during the visit. Week 100 PK sample should be taken after review of PK diary and pre-dose of CAB 30 mg+ABC/3TC. A second Week 100 and Week 128 PK sample will be collected approximately 2 hours after the last injection. i. Subjects will complete a diary only if the subject experiences a reaction ((E)pisodic). Subjects will be dispensed a new diary at each visit. Diary data will be entered into the eCRF. j. Q4W Injections are 1 x CAB LA 400 mg IM + 1 x RPV LA 600 mg IM.

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
																If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the week in which the subject's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is allowable for IM dosing but not preferred. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.** k. Or Long-Term Follow

Procedures for Extension - Q4W	W 100	W 101 [m]	W 104	W 108	W 112	W 116	W 120	W 121 [m]	W 124	W 128	W 132 [a]	W 136 [a]	W 140 [a]	W 144 [a]	WD [k, l]	Notes
																Up l. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the subject has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone. m. Procedures and visits for subjects who switch from oral to the optimized Q4W IM dosing regimen. n. At Week 100, oral Maintenance subjects eligible for extension dosing will take final dose of CAB 30 mg+ABC/3TC in the clinic within 2 hours of the optimized Q4W IM regimen. See Section 5.1.6 for IM dosing administration as loading doses are required.

Section 6.10.3.3 Liver Stopping Criteria - Rechallenge

Added clarifying statements to this section (additions underlined):

Subjects who meet liver toxicity stopping criteria should not be retreated with investigational product unless an exemption has been approved by the ViiV Safety and Labeling Committee (VSLC). The guideline for Rechallenge/Restart approved by the VSLC, which is maintained as a separate document (See Section 11.4, Appendix 4), must be followed.

Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug or continuation of LA dosing is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.

Subjects approved by the VSLC for restarting or re-dosing IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

See Section 11.4, Appendix 4 for further details.

Section 6.10.6.16 Seizures

New section added to protocol (underlined)

Seizures that occur on study should be managed according to the local guidelines on emergency seizure management which may include treatment with benzodiazepines, general supportive treatment, exclusion of metabolic and toxicological abnormalities using laboratory tests, and septic workup and excluding underlying structural abnormalities with neuroimaging.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses.

Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate eCRF page.

Section 6.10.14 Prompt Reporting of Serious Adverse Events and Other Events to GSK

Updated table with the following row (Seizure or suspected seizure - underlined):

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Cardiovascular (CV) or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
PRSAE	1 week	PRSAE data collection tool	1 weeks	Updated PRSAE data collection tool
Suspected ABC HSR[3]	24 hours	ABC HSR eCRF	1 Week	Updated ABC HSR eCRF
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities see Section 6.10.3[1,2]:				
ALT≥3xULN plus Bilirubin≥2xULN (35% direct)	24 hours	SAE data collection tool Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable	24 hours	Updated SAE data collection tool Updated Liver Event eCRF
ALT≥5xULN that persists ≥2 weeks	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF
ALT ≥8xULN	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT ≥3xULN or ALT ≥3 fold increase from Baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours	Liver Event eCRF	24 hours	Updated Liver Event eCRF

1. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety.
2. Liver Event Documents (i.e., "Liver Event eCRF" and "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.
3. ABC HSR eCRF required only if event meets one of the ICH-E2A, 1994 definitions of seriousness (see Section 6.10.6.14.2).

Section 6.11 Pharmacokinetics

Updated paragraph (changes struck through and underlined)

Plasma samples for determination of ~~GSK1265744~~ CAB and ~~TMC278~~ RPV concentration will be collected throughout the Maintenance Period and from Week 100 – Week 128 in the Extension Period of the study for subjects switching from oral Maintenance period regimen to the optimized IM dosing regimen of their choice. Additional samples will be collected for storage during the Extension and Long-Term Follow Up Period. Samples for determination of RPV will be protected from light until analyzed.

Section 6.11.1 PK Sample Collection

Updated table with Extension Period PK collection times (underlined)

Group	Analyte	Week	Sample Times Relative to Dose
IM	~~GSK1265744~~ CAB	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48 100* (prior to LA and last oral Maintenance dose), 104*, 108*, 112*, 116*, 120*, 124* and 128*	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40, 48, 100*, 104*, 112*, 120* and 128* Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 100*, 104*, 108*, 112*, 116*, 120*, 124* and 128* 2 Hours Post Dose: Day 1, Weeks 32, 48, 100*[a] and 128*[a] 1 Week Post Dose: Week 1, Weeks 25, 41, 101*[a] and Week 121*[a] 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
	~~TMC278~~ RPV	Day 1 (prior to LA and last oral Induction dose), Weeks: 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 41, 44 and 48 100* (prior to LA and last oral Maintenance dose), 104*, 108*, 112*, 116*, 120*, 124* and 128*	Pre-Dose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40, 48, 100*, 104*, 112*, 120* and 128* Pre-Dose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 100*, 104*, 108*, 112*, 116*, 120*, 124* and 128* 2 Hours Post Dose: Day 1, Weeks 32, 48, 100*[a] and 128*[a] 1 Week Post Dose: Week 1, Weeks 25, 41, 101*[a] and Week 121*[a] 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44
Oral	~~GSK1265744~~ CAB	Day 1, Weeks: 32 and 48	Pre-Dose: Day 1, Weeks 32 and 48
	~~TMC278~~ RPV	Day 1	Pre-Dose: Day 1

* Denotes PK sample times for subjects in the Extension Period. Samples will be placed in storage.

a. PK sample time for subjects switching from oral to an optimized IM dosing regimen only.

Section 6.11.2 Rationale of PK Sampling Strategy

Updated paragraph (changes struck through and underlined)

Given that PK data has been collected following oral administration of ~~GSK744~~ CAB and RPV (LAI116482), there will be no sampling during the Induction Period of the study. Blood sampling for ~~GSK1265744~~ CAB and ~~TMC278~~ RPV concentrations will be performed during the Maintenance ~~Period~~ and Extension Periods of the study to evaluate PK in HIV infected subjects. The proposed PK visits and sampling scheme at each visit presented in Table 4 is based on consideration of available PK data to support interim and final PK and PK/Pharmacodynamic (PD) analysis planned in this study.

Section 8.3.1.6 Extension Switch Population

Added new section to protocol (underlined)

The Extension Switch population will include all subjects randomized to the oral 30 mg + ABC/3TC arm who switch to and receive at least one dose of the optimized IM dosing regimen of their choice (either Q8W or Q4W) in the Extension Period.

The Extension Switch population will be used to evaluate safety and efficacy of the optimized IM dosing regimens during the Extension Period.

Section 8.3.4 Interim and Final Analysis

Updated section name (changes struck through and underlined)

~~Interim and Final~~ Planned Analysis

Section 8.3.4.1 IDMC Interim Analyses

Updated paragraph (changes struck through and underlined)

The purpose of these analyses is for the ~~Independent Data Monitoring Committee (~~IDMC~~)~~ to evaluate the efficacy, safety and tolerability of ~~GSK1265744~~ CAB at early time points in the study~~.~~ and to monitor the occurrence of protocol defined virologic failure in subjects switching from oral CAB 30 mg +ABC/3TC to an optimized IM dosing regimens during the Extension Period.

The IDMC intends to review at least one analysis before all eligible subjects have transitioned from the Induction Period to the Maintenance Period, or as soon as reasonably possible after subjects begin to enter the Maintenance Period. Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter, with IDMC agreement.

All of the IDMC reviews will be produced by a Statistics and Data Analysis Centre (SDAC).

Section 8.3.4.2 Futility Interim Monitoring

Added the following line (underlined)

Continuous monitoring of the number of protocol defined virologic failures for subjects switching from oral CAB 30 mg + ABC/3TC to the optimized IM dosing regimen of their choice (Q8W or Q4W) will also be monitored during the Extension Period.

Updated language (changes struck through and underlined)

...If the true rate of virologic failure is 3%, the probability ~~to see~~ that the number of ~~virology failure~~ virologic failures observed will exceed the threshold is less than<1%. Further details on this method are contained in the IDMC charter. Each threshold represents strong evidence in favour of H_0 over H_1 [Royall, 1997].

Added the following paragraph and table to section (underlined)

The number of protocol defined virologic failures will also be monitored in subjects switching from oral CAB 30 mg + ABC/3TC to the optimized IM dosing regimen of their choice (Q8W or Q4W) during the Extension Period. For subjects that have at least 4 weeks of treatment with an optimized IM dosing regimen, if the number of protocol defined virologic failures meets or exceeds the thresholds specified in the table below (Table 7) prior to all subjects completing Week 152, this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review. If an inadequate response is seen in any arm and it is determined by IDMC that that arm should be discontinued, then subjects on that treatment arm can be switched to the remaining IM dosing regimens.

Table 7 Number of protocol-defined virologic failures for each Extension Period optimized IM dosing regimen that constitutes strong evidence of inadequate virologic response – Subjects switching from Maintenance oral CAB + ABC/3TC only

Number of subjects with at least four weeks of IM dosing	**Number of protocol-defined virologic failures needed to trigger IDMC review**
3-21	>=3
22-32	>=4
33-43	>=5
44-54	>=6

Section 8.3.4.6 Week 96 Analysis

Changed section name (changes struck through)

Week 96 ~~Final~~ Analysis

Section 8.3.4.7 Week 128 Extension Switch Analysis

Added new section to protocol (underlined)

The Week 128 analysis will be conducted once the last randomized subject has completed the Week 128 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the efficacy, tolerability, and safety of optimized IM dosing regimens for subjects switching from the oral regimen therapy at the end of the Maintenace Period.

Section 8.3.4.8 Week 152 Analysis

Added new section to protocol (changes struck through and underlined)

The Week 152 analysis will be conducted once the last randomized subject has completed the Week 152 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the following: (a) the long-term safety and efficacy profile of both IM dosing regimens for subjects who continued randomized IM dosing in the Extension Period and (b) the safety, tolerability and durability of antiviral response of the optimized IM dosing regimens for subjects switching from the oral regimen therapy at the end of the Maintenace Period.

Follow-up analyses after the Week ~~96 analysis of data collected after subjects have switched to the chosen dose of GSK744 LA~~ 152 analysis may be conducted to more fully characterize the long-term safety and efficacy profile of ~~GSK744~~ CAB LA + RPV LA dosing regimens.

Section 8.3.5.1 Efficacy Analyses

The following changes were made to the section (changes struck through and underlined)

... Data collected from extra visits within a window will be included in the derivation of the time to ~~loss of~~ protocol defined virologic ~~response (TLOVR)~~ failure, but summary tables using OC datasets will only use the data captured closest to the target visit date.

... In addition, an OC analysis ~~will~~ may be performed for supportive purposes.

References

Updated the Rilpivirine Investigator's Brochure effective date from November 2013 to April 2016.

Amendment 7

Updated Exploratory Objectives, Primary Analysis, Discussion of Design, Futility Interim Monitoring, and Week 160 Interim Analysis sections to support an interim analysis at Week 160.**Section 2 Objectives and EndpointsExploratory**	
To evaluate the efficacy, tolerability, and safety of optimized IM dosing regimens CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Weeks 128 and ~~152~~ 160 for subjects switching from the oral regimen therapy at the end of the Maintenace Period. To evaluate the long term efficacy, tolerability, and safety of IM dosing regimens CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks at Week ~~152~~ 160 for subjects who continued randomized IM dosing in the Extension Period.	Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 128 and ~~152~~ 160 (Missing, Switch or Discontinuation = Failure, Extension Switch population) Proportion of subjects with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 128 and 160 using the FDA Snapshot algorithm (Extension Switch population) Proportion of subjects with protocol defined virologic failures over time Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.Absolute values and changes in CD4+ cell counts over time Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death). Incidence and severity of AEs and laboratory abnormalities over time. Absolute values and changes in laboratory parameters over time.

Section 3.2.9 Primary Analysis The primary analysis will be conducted when all subjects have completed their Maintenance Period Week 32 visit. This analysis will characterize the safety, tolerability and durability of antiviral response from both the Induction Period and the Maintenance Period. Planned analyses will also be conducted at Week 48, Week 96, Week 128 and Week ~~152~~ 160. Follow-up analyses of data collected after subjects have entered into the Extension Period may be conducted to more fully characterize the long-term safety and efficacy profile of CAB and RPV.

Section 3.3 Discussion of Design

… A Week ~~152~~ 160 analysis will permit an evaluation of the ability of the randomized and optimized investigational two-drug long-acting combinations to showcase long-term durability of virologic suppression. Additional long-term safety and efficacy data for all IM dosing regimens will be generated.

Section 8.3.4.2 Futility Interim Monitoring

…The number of protocol defined virologic failures will also be monitored in subjects switching from oral CAB 30 mg + ABC/3TC to the optimized IM dosing regimen of their choice (Q8W or Q4W) during the Extension Period. For subjects that have at least 4 weeks of treatment with an optimized IM dosing regimen, if the number of protocol defined virologic failures meets or exceeds the thresholds specified in the table below (Table 7) prior to all subjects completing Week ~~152~~ 160, this will be considered strong evidence of an inadequate response and will trigger a comprehensive IDMC data review. If an inadequate response is seen in any arm and it is determined by IDMC that that arm should be discontinued, then subjects on that treatment arm can be switched to the remaining IM dosing regimens.

Section 8.3.4.8 Week ~~152~~ 160 Analysis

The Week ~~152~~ 160 analysis will be conducted once the last randomized subject has completed the Week ~~152~~ 160 study visit and the database has been cleaned and released for analysis. The results of this analysis will be used to characterize the following: (a) the long-term safety and efficacy profile of both IM dosing regimens for subjects who continued randomized IM dosing in the Extension Period and (b) the safety, tolerability and durability of antiviral response of the optimized IM dosing regimens for subjects switching from the oral regimen therapy at the end of the Maintenace Period.

Follow-up analyses after the Week ~~152~~ 160 analysis may be conducted to more fully characterize the long-term safety and efficacy profile of CAB LA + RPV LA dosing regimens.