TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	ING200336: A Prospective, Interventional Pharmacokinetic and Safety Study of DTG/ABC/3TC in Pregnant Women

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N166290_00	2013-DEC-18	Original
2013N166290_01	2014-APR-15	Amendment No.: 01
Editorial changes, including corrections of minor typographical errors and/or inconsistencies in the Time and Events Table 6 and the protocol, inclusion of infant HIV status if available, and edits to Appendix 3 wording		
2013N166290_02	2014-APR-23	Amendment No. 02
Correction of typographical errors in Amendment 1: Specifically, in the Summary of Revisions, page 1, the reader is referred to Time and Events Table 6; it should be Table 4. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was added as a new appendix, changing numbers of other appendices. It's inclusion also needed to be added to Appendix 6. Lastly, where the Summary of Revisions says Appendix 3, it should be Appendix 4.		
2013N166290_03	2018-JUN-19	Amendment No. 03
Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir at the time of conception. • The Rationale and Risk Assessment sections (Section 1.2. and Section 1.3.1.) were updated to include language regarding risk and mitigation of neural tube defects. • The Withdrawal Criteria (Section 4.5.) were updated to include a reminder that post-delivery, subjects who desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, should be withdrawn from the study. • The Time and Events table (Section 6.) was updated to include a footnote to clarify the requirement for pregnancy tests post-delivery, and a reminder for investigators to check at every post-delivery visit that subjects are avoiding pregnancy. • Contraception Requirements for the Post-Partum and Continuation Phases (Section 6.5.4.8.) were updated with the most recent list of 'highly effective methods for avoiding pregnancy in females of reproductive potential', which excludes the double barrier method of contraception. Administrative updates were made.		

SPONSOR SIGNATORY

PPD

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Date

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SPONSOR INFORMATION PAGE

Clinical Study Identifier: 200336

This study is sponsored by ViiV Healthcare LLC. GlaxoSmithKline is responsible for implementing and managing all aspects of this study. The study is performed in compliance with Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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Regulatory Agency Identifying Number(s): US IND 75,382; EudraCT 2013-003527-11

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200336

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

µg	Microgram
3TC	Lamivudine, EPIVIR™
AAG	Alpha-1 acid glycoprotein
ABC	Abacavir, ZIAGEN™
AE	Adverse Event
AGA	Adequate gestational age
ALT	Alanine Aminotransferase
APR	Antiviral Pregnancy Registry
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC(0-24)	Area under the concentration-time curve during a 24-hour interval at steady state
BID	Twice Daily
BUN	Blood urea nitrogen
Cτ	Drug concentration at the end of dosing interval
c/mL	Copies/milliliter
C0	Drug concentration immediately prior to dosing at steady state
Caverage	Average Concentration
CC	Calcium carbonate
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
Cmax	Maximal drug concentration
Cmin	Minimal drug concentration
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug Induced Liver Injury
dL	Decilitre
DTG	Dolutegravir
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFD	Embryo Fetal Development
EFV	Efavirenz
ELV	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed dose combination
FF	Ferrous Fumarate
FRP	Females of Reproductive Potential
FTC	Emtricitabine
FU	Follow-up

g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
HELLP	Hemolysis, elevated liver enzymes and low platelet count
HIV-1	Human Immunodeficiency Virus type 1
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INI	Integrase Inhibitor
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
LBW	Low Birth Weight
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LGA	Large gestational age
LLOD	Lower Limit of Detection
mg	Milligrams
mL	Millilitre
MSDS	Material Safety Data Sheet
MTCT	Mother-to-Child Transmission
NOAEL	No adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PGx	Pharmacogenetics
PI	Protease Inhibitor
PK	Pharmacokinetic
PMTCT	Prevention of Mother-to-Child Transmission
QWBA	Quantitative Whole Body Autoradiography
RAL	Raltegravir
RAP	Reporting Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic Acid
RTV	Ritonavir
SAE	Serious Adverse Event
SGA	Small gestational age
SJS	Stevens Johnson Syndrome
SoC	Standard of Care

SPM	Study Procedures Manual
SRT	Safety Review Team
t1/2	Half-life
TDF	Tenofovir disoproxil fumarate, Viread
TEN	Toxic Epidermal Necrolysis
tmax	Time to observed maximal drug concentration
ULN	Upper Limit of Normal
US	United States
Vss/F	Steady state volume of distribution
WBC	White Blood Cell
WD	Withdrawal
ZDV	Zidovudine, Retrovir

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PROTOCOL SUMMARY

Rationale

In this protocol, the dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed dose combination (FDC) tablet is being made available to women who become pregnant while participating in study ING117172. Continuation of antiretroviral therapy (ART) is key to both mother and the unborn fetus in order to maintain virologic suppression in the mother (thereby decreasing the risk for maternal disease progression), but also to reduce the risk of maternal-fetal transmission of human immunodeficiency virus type 1 (HIV-1) to her unborn child.

This study also offers the first opportunity to investigate the impact of pregnancy on DTG pharmacokinetics (PK).

Objective(s)

Primary

Mother:

- To describe the total plasma DTG PK parameters with the DTG/ABC/3TC FDC during Weeks 18-26 and Weeks 30 to 36 of the pregnancy and 8-12 weeks postpartum;
- To characterize the safety and tolerability of DTG/ABC/3TC FDC when used during pregnancy.

Secondary

Mother:

- To assess the antiviral activity of the DTG/ABC/3TC FDC when administered during pregnancy;
- To assess the immunologic activity of DTG/ABC/3TC FDC;
- To assess the incidence of treatment-emergent genotypic and phenotypic resistance in subjects who meet virologic withdrawal criteria;
- To evaluate the unbound DTG concentrations in plasma during Weeks 18-26 and Weeks 30-36 of the pregnancy and 8-12 weeks postpartum;
- To compare the DTG concentrations from cord blood with those in maternal plasma at the time of delivery;
- To characterize birth outcomes;

- To characterize pregnancy outcomes.

Infant:

- To characterize infant outcomes at birth.

Study Design

ING200336 is an open-label Phase IIIb, prospective, interventional, study to evaluate PK and safety, as well as birth outcomes in pregnant women while receiving treatment with the fixed dose combination tablet of DTG/ABC/3TC once daily. The study will be conducted by the HIV provider, therefore, it will be necessary for the HIV provider to communicate with, and coordinate collection of, obstetric data with the subject's pregnancy provider (ie., obstetrician or mid-wife). Eligible subjects are HIV-1 infected women participating in study ING117172 who become pregnant and are required to be withdrawn from that study. The number of women that will be enrolled into this protocol cannot be established *a priori*, as unintended pregnancies cannot be determined in advance. The maximum number of women would include women randomized to DTG/ABC/3TC FDC in ING117172 (n ~237), though unintended pregnancies in all of those women would not be anticipated. Based on pregnancy rates from two recent DTG studies in ART-naive women, the anticipated rate of unintended pregnancy over 48 weeks would be approximately 5% (n ~12) [GlaxoSmithKline Document Number RM2011N118494_00, GlaxoSmithKline Document Number RM2011N117164_01]. If 12 subjects were to enroll in ING200336, at least 8 subjects providing evaluable DTG PK parameters during Weeks 18-26, Weeks 30-36 and Weeks 8-12 postpartum would be needed to estimate PK parameters with adequate accuracy.

Key objectives of the study are to characterize DTG PK parameters following treatment with the DTG/ABC/3TC FDC based on intensive sampling during pregnancy (Weeks 18-26 and Weeks 30-36) and postpartum (8-12 weeks post delivery), to characterize pregnancy outcomes, birth and infant outcomes, and to further characterize the safety, tolerability and antiviral activity of DTG/ABC/3TC FDC when used during pregnancy. All study subjects will continue to receive DTG/ABC/3TC FDC through the 8-12 weeks post partum visit. Subjects are considered to have completed the study after completing the postpartum evaluation. Women may continue to receive DTG/ABC/3TC FDC after study completion (in which case they will be followed q12weeks) until study medications are locally approved and commercially available, the subject meets a protocol-defined reason for discontinuation or until they no longer receive clinical benefit.

The primary outcome analyses will take place after the last subject enrolled gives birth and completes their last visit. As this study will remain open until ING117172 is closed, additional analyses of data may be conducted in this open label study prior to this timepoint as required by the Sponsor (e.g., when an adequate number of subjects with PK data are available, or for regulatory filings).

Subjects will participate in a short screening period which includes an assessment for potential pregnancy complications (e.g., hypertension, diabetes, and underlying infections.) and a thorough obstetric history (including gravidity, previous complications

and/or risks, etc.). Any subject who became pregnant and who meets the virologic withdrawal criteria in ING117172 will not be eligible to participate in this study. Because obstetric care will not be specifically provided via this study the subject must also establish appropriate obstetric care per local standard of care (SoC). It will be necessary for the subject to be willing to share medical information, as necessary, to the HIV investigator for both herself and her infant to facilitate collection of delivery, birth and infant outcomes by the investigator.

Once the subject learns she is pregnant, there are two scenarios for enrollment:

1. If the subject wants to enter the pregnancy study, and has been seen within 28 days for a regularly scheduled ING117172 visit, the site would schedule a Withdrawal visit, which still must remain within the 28 day window of the visit when pregnancy was documented. The previous visit results will be used as the "screening visit" to qualify the subject for enrollment and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336. A urine pregnancy test, as well as a urine dipstick to check for protein, must be performed on Day 1.
2. If the subject is determined to be pregnant outside of a study visit and wants to enter ING200336 but has not been seen within the 28 day window, the site is to perform an unscheduled ING117172 visit to collect adverse events/serious adverse events (AEs/SAEs), plasma HIV-1 RNA and laboratory results, including a serum pregnancy test, as well as a urine dipstick to check for protein, in order to document the subject's current medical status. If the pregnancy is confirmed, the site would then schedule the Withdrawal visit within 28 days of the unscheduled visit. The unscheduled visit results will be used to qualify the subject for enrollment (i.e., is the screening visit) and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336.
3. In both scenarios the Withdrawal visit for ING117172 will also be Day 1 for ING200336 to ensure no disruption in provision of study treatment. In the event the subject miscarries or electively terminates the pregnancy prior to Day 1 (Baseline) of ING200336, she must still be discontinued from ING117172 and followed per the requirements of ING117172 and may not continue enrollment into study ING200336.

In both of these scenarios new demographic, Baseline characteristics, concomitant medications, medical history and HIV associated conditions will be collected on Day 1, as well as an obstetric history.

If there is an ongoing, unresolved AE and/or SAE at the time of the Withdrawal visit in ING117172 the AE/SAE will be followed for event outcome, which will be recorded in the eCRF, as part of ING117172 (i.e., followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up). The AE/SAE will be transcribed as medical history in ING200336. Any exacerbation or worsening of the AEs and/or SAEs from ING117172 during subject participation in

ING200336, will be recorded as a new entry in the AE or SAE eCRF pages for ING200336 with a start date reflecting the clinical worsening, and will not be recorded for ING117172. All SAEs (including those 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 or ViiV concomitant medication) and any non serious AEs of special interest (defined in the study procedure manual) occurring from the withdrawal visit in ING117172 through to administration of IP at Day 1 of ING200336, will be recorded in the eCRF for ING117172.

All AEs and SAEs occurring from Day 1 in ING200336 through to the follow up contact will be collected and recorded in the eCRF for ING200336, regardless of relationship to study participation or any other causality.

After all ING117172 Withdrawal procedures have been completed subjects who fulfil eligibility requirements may be enrolled. Subjects will begin Day 1 and will continue to receive DTG/ABC/3TC FDC treatment in an open-label fashion in ING200336. During the second trimester (Weeks 18-26) of pregnancy, the third trimester (Weeks 30-36) of pregnancy, as well as postpartum (8 -12 weeks post delivery), subjects will undergo intensive PK visits. Serial plasma samples will be collected during each PK visit for the determination of DTG (total and unbound) concentrations. All subjects will participate in a postpartum evaluation, including the PK assessment, 8-12 weeks post delivery. Subjects will continue to have access to DTG/ABC/3TC FDC postpartum until it is either locally approved and commercially available, the patient no longer derives clinical benefit, the patient meets a protocol-defined reason for discontinuation, or development of DTG/ABC/3TC FDC is terminated.

Given the requirement that subjects who become pregnant on ING117172 be withdrawn from the study, sites that are interested in enrolling pregnant women from ING117172 onto ING200336 should seek IRB/EC approval for ING200336 in advance of identifying such subjects, in order that DTG/ABC/3TC FDC treatment may be continued without interruption.

Study Endpoints/Assessments

No formal hypothesis testing will be performed. Summarized data will provide only descriptive information regarding outcomes.

The primary outcome measure for this study will be to evaluate the PK (area under the concentration-time curve during a 24-hour interval at steady state [AUC_{24}], maximal drug concentration [C_{max}], drug concentration at the end of dosing interval [C_{τ}], apparent clearance [CL/F[, steady state volume of distribution [Vss/F] and the half life [t½]) of DTG during Weeks 18-26, Weeks 30-36 of the third trimester of pregnancy and at 8-12 weeks postpartum. The study will also evaluate maternal and pregnancy outcomes and characterize the tolerability of DTG/ABC/3TC FDC when administered during pregnancy. Secondary outcomes include PK ($T_{max,}$ $C_{0),}$ unbound concentrations at 3 and 24 hours post dose in the third trimester and postpartum, plasma DTG concentration in cord blood and maternal plasma at the time of delivery, efficacy measures (including proportion with HIV-1 RNA < 400 c/mL and HIV-1 RNA < 50 c/mL over time, and absolute values and change from Baseline in CD4+ cell counts over time). Infant

outcomes, pregnancy outcomes, and maternal AEs and laboratory parameters will be assessed to to characterize the safety and tolerability of DTG/ABC/3TC FDC administered during pregnancy. Virology endpoints will include an assessment of the development of viral resistance in subjects meeting confirmed virologic withdrawal criteria.

1. INTRODUCTION

Pregnancy increases the risk of HIV progression, while HIV increases the risk for maternal complications from pregnancy and poses the risk of perinatal HIV transmission to the unborn fetus. Mother to child transmission (MTCT) of HIV can occur during pregnancy, labor, delivery or postpartum through breastfeeding. In the absence of any interventions, vertical HIV transmission rates approximate 35%, but fall below 5% with effective interventions [WHO, 2010]. In the United States and other developed countries, the risk of perinatal infection has decreased from 25% without intervention to less than 2% with intervention [WHO, 2012]. The HIV-infected mother who breastfeeds her infant while taking ARVs herself or giving ARVs to her infant reduces the risk of transmission to about 2% after 6 months of breastfeeding, or 4% over 12 months (UNAIDS, 2011).

The 2013 WHO Guidelines thus recommend (strong recommendation, moderate-quality evidence) all pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (WHO, 2013).

The ART recommendation for pregnant women prioritizes the health of women over potential risks and increased cost. For women who are on ARV therapy at the time that they become pregnant, the World Health Organization (WHO) recommends that women continue such therapy if they are responding to the ARV.

In line with this recommendation, this study will allow those women participating in ING117172 who are virologically responding to dolutegravir/abacavir/3TC fixed dose combination tablet (DTG/ABC/3TC FDC) but become pregnant on study, to continue DTG/ABC/3TC FDC in order to maintain their effective regimen with minimal disruption. The objective of ING200336 is to describe the pharmacokinetics (PK) of DTG, characterize the safety of DTG/ABC/3TC FDC administered during pregnancy, and to characterize maternal, birth and infant outcomes following treatment with DTG/ABC/3TC FDC.

1.1. Background

The global benefits anticipated from ART in pregnant women who are eligible for treatment include treatment of the mother's underlying HIV disease, eliminating pediatric transmission/infection and reducing sexual transmission of HIV. However, pregnancy impacts all components of drug disposition – absorption, distribution, metabolism, and excretion. These physiological changes in pregnancy can result in measurable changes in drug disposition, and in some cases necessitate dose administration adjustments.

ABC and 3TC

Both ABC and 3TC have been studied during pregnancy. 3TC, used frequently during pregnancy as a component of lamivudine/zidovudine [3TC/ZDV]; COMBIVIR™),

[PETRA, SAINT studies] crosses the placenta by simple diffusion, and the median ratio of 3TC concentration in maternal plasma at the time of delivery and cord blood is around 1 [Bloom, 1997; Mandelbrot, 2001]. 3TC accumulates in amniotic fluid where the concentration at the time of delivery is 5-fold more than maternal plasma concentration without an impact on pregnancy outcomes [Bloom, 1997]. Pregnant women can receive the once daily adult dose of 3TC (300 mg once daily).

A Phase I study of abacavir (ABC) in pregnant women indicated that the area under the time concentration curve (AUC) drug concentration during the third trimester of pregnancy is similar to the drug concentration observed at 6 and 12 weeks postpartum, and to concentrations observed in non-pregnant females [Best, 2006]. Cord blood ABC concentrations averaged 110% of maternal plasma concentration at the time of delivery. Pregnant women can receive the adult dose of ABC (600 mg once daily).

Data are available on association between ABC and 3TC exposure in women during pregnancy and birth outcomes. The Antiretroviral Pregnancy Registry (APR), an international, voluntary, prospective cohort study, provides an early signal of teratogenicity associated with prenatal ARV use. Using APR data on 13,537 prospectively reported singleton pregnancies from HIV-infected women, frequency estimates of adverse birth outcomes in women a) exposed to ABC containing regimens compared to those exposed to non-ABC ARV regimens and b) exposed to 3TC containing regimens compared to those exposed to non-3TC ARV regimens were undertaken.

Of 1864 outcomes with ABC exposure, 1782 (95.6%) were live births and 82 (4.4%) resulted in spontaneous/induced abortions or still births. Among live births 16.2% had low birth weight (LBW), 11.7% were preterm, and 3% had birth defects. Of 11,673 outcomes with non-ABC exposure, 11,049 (94.7%) were live births and 624 (5.3%) resulted in spontaneous/induced abortions or still births. Among live births, 16% had LBW, 12.5% were preterm, and 2.9% had birth defects. The odds ratios comparing exposure to ABC-containing to non-ABC ARV regimen were, for spontaneous abortion 0.96 (95% confidence interval [CI] 0.67-1.36); induced abortion 0.82 (95%CI: 0.56-1.21); still birth 0.60 (95%CI: 0.35-1.03); preterm birth 0.93 (95%CI: 0.79-1.09), and LBW 1.02 (95%CI: 0.88-1.17).Of 10,531 outcomes with 3TC exposure, 10,032 (95.3%) were live births and 499 (4.7%) resulted in spontaneous/induced abortions or still births. Among live births 16% had LBW, 11.8% were preterm, and 3% had birth defects. Of 3006 outcomes with non-3TC exposure, 2799 (93.1%) were live births and 207 (6.9%) resulted in spontaneous/induced abortions or still births. Among live births 16% had LBW, 14.5% were preterm, and 2.8% had birth defects. The odds ratios comparing exposure to 3TC-containing to non-3TC ARV regimen were, for spontaneous abortion 0.63 (95%CI: 0.49-0.82); induced abortion 0.54 (95%CI: 0.42-0.70); still birth 1.19 (95%CI: 0.81-1.74); preterm birth 0.79 (95%CI: 0.70-0.89), and LBW 1.00 (95%CI: 0.88-1.12). There was also no difference in the incidence of LBW, prematurity, or birth defects, and no specific pattern of birth defects has been discerned for either ABC or 3TC containing regimen [Vannappagari, 2013].

In a randomized controlled clinical study data of ABC exposure during pregnancy and breast-feeding [Powis, 2011], 560 HIV-1 infected pregnant women with CD4+ ≥200

cells/mm^3 were randomly assigned to receive co-formulated ABC, zidovudine (ZDV), and 3TC (TRIZIVIR™, the nucleoside reverse transcriptase inhibitor [NRTI] group, n=285) or lopinavir−ritonavir plus zidovudine−lamivudine (lopinavir−ritonavir + COMBIVIR: the protease inhibitor [PI] group n=275) from 26 to 34 weeks' gestation through planned weaning by 6 months post partum. A further 170 women with CD4+ < 200 cells per cubic millimeter (mm^3) received nevirapine plus Combivir (the observational group). Infants received single-dose nevirapine at birth and ZDV from birth through 4 weeks.

There were 709 live-born infants (283 nucleoside reverse transcriptase inhibitor (NRTI) group, 270 protease inhibitor (PI) group, and 156 observational group) and 24 stillbirths [8 in the nucleoside reverse transcriptase inhibitor (NRTI) group (3%), 5 in the PI group (2%), and 11 in the observational group (7%)]. Although not powered to detect MTCT differences between the treatment groups, the overall rates of MTCT were low: by 6 months of age, 8 of 709 live-born infants (1.1%) were infected [6 in utero (4 NRTI group, 1 PI group and1 observational group)], and 2 were infected during the breast-feeding period (both in NRTI group). Treatment-limiting AEs occurred in 2% of women in the NRTI group, 2% in the PI group, and 11% in the observational group.

Congenital abnormalities were reported in 5 infants in each group and included polydactyly (6), undescended testis (7), dextrocardia (1), and hydrocephalus (1); all were determined to be "not related" or "probably not related" to study drugs [Shapiro, 2010]. Prematurity was more common in the PI group than the NRTI group (23% vs. 15%). The proportion of infants with low birth weight did not differ significantly (13% NRTI, 17% PI and 15% in the observational group [Powis, 2011].

Thus, the risks of ABC and 3TC during pregnancy appear no greater than that associated with alternative regimens.

Dolutegravir (DTG)

No studies have been conducted with DTG in pregnant women as pregnant women were excluded from the Phase IIb/III DTG clinical studies and subjects who became pregnant were required to discontinue from the studies. Forty one pregnancies were reported across the DTG clinical studies and compassionate use program through 26Oct2013; 25 for DTG- containing ART and 16 for comparator. Thirty-two of the pregnancies were reported in the ART-naïve population (17 were exposed to DTG [16 in female subjects directly receiving DTG and one in a partner potentially exposed to DTG via the semen of a male subject], 7 on efavirenz/tenofovir/emtricitabine [EFV/TDF/FTC], 6 on raltegravir [RAL], and 2 on darunavir+ritonavir [DRV+RTV]). Five were reported in the ART-experienced (integrase inhibitor [INI]-naïve) population (4 on DTG- and 1 on RAL-containing ART). Three were reported in the ART experienced (INI- resistant) population (DTG) and one was reported in a completed Phase I, healthy volunteer study (DTG).

Of the 41 pregnancies, 15 resulted in delivery of a normal healthy baby (including the partner pregnancy), 12 in elective termination, one was ectopic (EFV/TDF/FTC) and 6 resulted in spontaneous abortions (2 each for DTG and EFV/TDF/FTC and 1 each for RAL and DRV+RTV; all between 2 and 10 weeks gestation). In seven cases, the

pregnancy was either ongoing or unknown (5 on DTG and one each on EFV/TDF/FTC or DRV+RTV). For one of the ongoing pregnancies, involving an ART-experienced (INI-naïve) subject exposed to DTG plus abacavir, atazanavir and RTV, a routine ultra sound at 31 weeks gestation indicated a congenital anomaly of double outlet right ventricle with ventricular septal defect in the foetus, which was considered reasonably attributable to IP by the reporting investigator. However, this finding has not yet been confirmed post-partum. The subject was exposed to IP for approximately 75 weeks before conception and approximately 6 weeks post her date of last menstrual period, before being permanently discontinued from IP and withdrawn from the study due to the pregnancy. Thus the foetus was exposed to DTG for approximately the first month of the first trimester. With the exception of this case, no other congenital anomalies have been reported.

To date there has been no preclinical findings or evidence for an increased risk for teratogenic effects for DTG. The overall nonclinical reproductive and developmental toxicity profile for DTG in rats and rabbits suggests that DTG is not teratogenic and has a low potential for fetal risk.

There were no effects on fertility or early embryonic development in rats orally administered DTG at ≤1000 mg/kg/day in males or females. The no adverse effect level (NOAEL) was 1000 mg/kg/day, which corresponds to ~33X the expected human exposure for a 50 mg once daily, based on gender averaged mean exposures achieved in the 4 week rat toxicity study.

No adverse effects on fetal development were observed in pregnant rats orally administered DTG at ≤1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was1000 mg/kg/day, which corresponds to ~38X the expected human exposure for a 50 mg once daily dose.

In an embryofetal development (EFD) study in rabbits, DTG was orally administered at 40, 200, or 1000 mg/kg/day to pregnant rabbits. Suppressed body weight gain (13.6% on gestation Day 19), decreased food consumption (up to 53%) and scant or no feces/urine associated with the decreased food consumption were noted in the 1000 mg/kg/day dams. Maternal toxicity at this dose precluded dosing DTG at higher doses in rabbits because maternal toxicity can confound teratogenicity assessment. Therefore, the dose of 1000 mg/kg/day was the maximal dose that could be administered in this embryo fetal development EFD study.

The NOAEL was 200 mg/kg/day for maternal general toxicity (~0.27X the expected human exposure for a 50 mg once daily dose) and 1000 mg/kg/day for maternal reproductive function and embryofetal development (0.56X the expected human exposure for a 50 mg once daily dose,). Of note, there were no teratogenic effects at 1000 mg/kg/day, a dose that exceeded the NOAEL for maternal toxicity.

In a pre-and postnatal development study, DTG was administered to female rats at doses of 5, 50 or 1000 mg/kg/day from Day 6 of gestation to Day 20 of lactation. Suppressed body weight gain and decreased food consumption were noted in dams (F0) in the 1000 mg/kg/day group during the lactation period, which were associated with mild

decreases in body weights in the offspring in the 1000 mg/kg/day group from pre-weaning until adolescence. There were no adverse effects on maternal pregnancy, parturition, lactation or offspring (F1) survival, behavioral or reproductive function. The NOAEL for maternal reproductive function was 1000 mg/kg/day (~32X above the expected human exposure for a 50 mg once daily dose, based on exposures achieved in female rats in the 4 week toxicity study). Due to the decreased body weights of the offspring observed at higher doses, the NOAEL for pre- and postnatal development of the offspring (F1) was 50 mg/kg/day. This is ~25X above the expected human exposure for a 50 mg once daily dose (extrapolated from gender mean exposures achieved in the rat 14 day toxicity study). Based on the fact that effects on offspring body weights were noted at doses where maternal toxicity was observed, and the presence of considerable safety margins expected at the proposed clinical doses, there is minimal risk for adverse effects on postnatal development in offspring of mothers receiving DTG.

DTG is excreted in the milk of lactating rats. Following oral administration (50 mg/kg) to lactating rats on Day 10 post partum, total radiocarbon concentrations in milk were up to 2-fold greater than those in maternal blood. The metabolite profile of milk indicated that parent DTG represented more than 95% of the total radiocarbon, consistent with the findings in plasma from female rats in an earlier study. These data suggest that F1 offspring in the pre- and postnatal toxicity study were exposed to the drug via the milk. Following oral administration of DTG (50 mg/kg) to pregnant rats on Day 18 post conception, DTG-related material was found, by quantitative whole body autoradiography (QWBA) analysis, to be widely distributed to the fetuses over the 24-hour sampling period. These data indicate that DTG is able to cross the placental barrier.

1.2. Rationale

Few studies have been conducted with DTG in pregnant women. DTG was not anticipated to increase the risk of adverse development or reproductive outcomes in humans. Recently, early results from an unplanned interim analysis of an ongoing birth outcome surveillance study in Botswana showed that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%. Extensive clinical data is available on ABC and 3TC, and this data suggests that the use of ABC and 3TC do not lead to adverse outcomes for the mother or baby when used in pregnancy. Additionally, for women who are already receiving, tolerating and responding virologically to DTG/ABC/3TC, there may be benefit in continuing the regimen after pregnancy is confirmed (if after the first trimester), as the mother may be more likely to continue a familiar and effective regimen. Additional PK, safety and efficacy data is required to further inform the use of DTG and DTG/ABC/3TC in pregnancy.

To date, the efficacy, PK, safety and drug interaction potential of DTG have been evaluated in an extensive program of Phase I to III clinical trials. Data are summarized in the current Investigator Brochure. In both ART-naïve and ART-experienced (INI- naïve) patients, the safety profile for DTG 50 mg once daily was comparable to raltegravir (RAL) and generally favorable to EFV/TDF/FTC and EFV (studies ING113086 [SPRING-2] and ING114467 [SINGLE], respectively). The most frequently observed adverse events (AEs) across patient populations were diarrhea, nausea, and headache,

which were generally Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. In treatment-naïve HIV-infected adult subjects, DTG 50 mg once daily was shown to be efficacious, and non-inferior to RAL in combination with a background regimen with dual NRTI [SPRING-2]. When used in combination with ABC/3TC (EPZICOM/KIVEXA™), DTG was shown to be superior to EFV/TDF/FTC, a result driven by better tolerability of the DTG based regimen [SINGLE]. Furthermore, DTG 50 mg once daily may have a higher barrier to resistance in INI-naive patients, as suggested in the treatment-experienced (INI-naive) SAILING study where significantly fewer virologic failures and significantly fewer subjects with INI resistance were observed when compared with RAL.

DTG is primarily metabolized through UGT1A1 with minimal renal excretion (<1% of total dose given orally). DTG is a drug with low clearance (~1 L/hr for CL/F after oral dosing), low volume of distribution (~12.5 L for Vd/F after oral dosing), and high plasma protein binding (>99%). The following physiologic changes during pregnancy may have impact on DTG PK (Table 1):

Table 1 Physiological Change During Pregnancy and Potential Impact on DTG Pharmacokinetics

Possible Physiological Changes During Pregnancy*	Potential Impact on DTG PK
Changes in total body weight and body fat composition.	Increase clearance (CL) as well as the volume of distribution (Vd)
Delayed gastric emptying and prolonged gastrointestinal transit time.	Increase oral bioavailability, delayed time to observed maximal drug concentration (tmax)
Increase in extra cellular fluid and total body water.	Increase Vd
Increased cardiac output, increased stroke volume, and elevated maternal heart rate.	Unlikely to have effect
Decreased albumin concentration with reduced protein binding.	Increase unbound fraction, CL, and Vd
Increased blood flow to the various organs (e.g., kidneys, uterus).	Unlikely to have effect
Increased glomerular filtration rate.	Unlikely to have effect
Changed hepatic enzyme activity, including phase I CYP450 metabolic pathways (e.g., increased CYP2D6 activity), xanthine oxidase, and phase II metabolic pathways (e.g., N-acetyltransferase).	May affect CL

*FDA Guidance for Industry (2004): Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling.

In previous studies DTG has not been prone to changes by demographic factors (age, gender, weight, etc) based on population PK analyses. Accumulated safety data showed that DTG is in general well tolerated and no PK/Pharmacodynamic (PD) relationship for safety measures has been identified. Therefore, despite the potential impacts of physiological changes on DTG PK, it is expected that DTG PK should not change

significantly during pregnancy. The clinical dose of 50mg once daily will be used in this study and no therapeutic drug monitoring is needed.

1.2.1. Drug Interactions

1.2.1.1. Use of Calcium and Iron Supplements with DTG: Study ING116898

Drug interactions relevant to the use of ABC and 3TC are described in approved product labels. A description of the drug interaction profile for DTG is included in the current IB; the recently completed interaction study for calcium and iron supplements is described below.

The PK effect of DTG 50 mg co-administered with a single dose of calcium carbonate (CC) 1200mg or ferrous Fumarate (FF) was evaluated in a Phase I, randomized, four-period crossover study (ING116898) in healthy adult subjects.

Twelve subjects were enrolled into one of the two cohorts and received each of four treatments in a randomized fashion: 1) A single dose of DTG 50 mg administered under fasted conditions; 2) A single dose of DTG 50 mg co-administered with a single dose of CC 1200 mg or FF 324 mg under fasted conditions; 3) A single dose of DTG 50 mg co-administered with a single dose of CC or FF with a moderate-fat meal; 4) A single dose of DTG 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of CC or FF. There was a washout period of at least 7 days between treatments. Serial PK samples were collected during each treatment period for the measurement of plasma DTG concentrations.

Under fasted conditions, co-administration of CC reduced DTG exposure by 37-39% and FF reduced DTG exposure by 54-57%; food (a moderate fat meal) and 2hr separation completely eliminated the negative effect of calcium carbonate on DTG exposure (See Table 2 and Table 3).

Table 2 Statistical Comparison of Plasma DTG Pharmacokinetic Parameters (Calcium Carbonate Cohort)

Comparison	Ratio of GLS Means (90% CI)			
	DTG + CC vs DTG Alone (fasted)	DTG + CC (fed) vs DTG Alone (fasted)	DTG 2hr prior to CC vs DTG Alone (fasted)	DTG + CC (fed) vs DTG+ CC (fasted)
AUC(0-t)	0.61 (0.48, 0.79)	1.10 (0.84, 1.43)	0.95 (0.73, 1.24)	1.79 (1.37, 2.33)
AUC(0-∞)	0.61 (0.47, 0.79)	1.09 (0.84, 1.43)	0.94 (0.72, 1.23)	1.78 (1.36, 2.33)
Cmax	0.63 (0.50, 0.81)	1.07 (0.83, 1.38)	1.00 (0.78, 1.29)	1.70 (1.32, 2.18)
C24	0.61 (0.47, 0.80)	1.08 (0.81, 1.42)	0.90 (0.68, 1.19)	1.76 (1.33, 2.33)

CI=confidence interval

Table 3 Statistical Comparison of Plasma DTG Pharmacokinetic Parameters (Ferrous Fumarate Cohort)

Comparison	Ratio of GLS Means (90% CI)			
	DTG + FF vs DTG Alone (fasted)	DTG + FF (fed) vs DTG Alone (fasted)	DTG 2hr prior to FF vs DTG Alone (fasted)	DTG + FF (fed) vs DTG+ FF (fasted)
AUC(0-t)	0.45 (0.37, 0.54)	0.98 (0.81, 1.19)	0.94 (0.78, 1.14)	2.18 (1.80, 2.64)
AUC(0-∞)	0.46 (0.38, 0.56)	0.97 (0.80, 1.19)	0.95 (0.78, 1.15)	2.12 (1.75, 2.58)
Cmax	0.43 (0.35, 0.52)	1.03 (0.85, 1.26)	0.99 (0.81, 1.21)	2.40 (1.97, 2.94)
C24	0.44 (0.36, 0.54)	0.99 (0.80, 1.22)	0.92 (0.74, 1.13)	2.25 (1.83, 2.77)

In summary, DTG can be given concurrently with calcium or iron supplements with food; without food, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG, ABC, 3TC and/or ABC/3TC FDC can be found in the most current version of the DTG Investigator's Brochure (IB) and the approved labels for ABC and 3TC. The following section outlines the risk assessment and mitigation strategy of the DTG/ABC/3TC FDC in this protocol.

1.3.1. Risk Assessment

There are no shared metabolism pathways between the components of DTG/ABC/3TC, and no common target organs were identified in respective pre-clinical studies. As such, there is no pharmacologic data that would predict increased safety risk for the DTG/ABC/3TC FDC formulation beyond that identified for the individual active moieties DTG, ABC and 3TC. Early in clinical development, no drug-drug interaction between DTG and ABC/3TC was apparent given the safety and efficacy profile observed in the Phase IIb study ING112276 [SPRING-1] in which 67 subjects received DTG in combination with ABC/3TC for up to 96 weeks. Clinical safety data from the subjects treated with DTG + ABC/3TC in the Phase IIIa studies ING114467 [SINGLE] and study ING113086 [SPRING-2] were consistent with the safety profile of the individual active moieties.

Risks in ING200336 are primarily related to those that accrue to the fetus with regards to the DTG/ABC/3TC FDC regimen, and the risks associated with unknown effects of pregnancy on DTG exposure. ABC and 3TC do not pose additional safety risks to women beyond those recognized for all patients in the approved country product label for the ABC/3TC FDC [Vannappagari, 2013], and as noted above, ABC and 3TC have been given to pregnant women without increased adverse outcomes for the mother or baby. For DTG, risks to the mother are outlined in the most current DTG IB [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]; no effect of gender on safety profile of DTG has been

observed (beyond what might be expected; e.g., more anaemia in women). It is unknown at this time if the physiologic differences experienced in pregnancy would amplify particular risks identified with DTG, but based on the recognized risks and absorption/distribution/metabolism/excretion of DTG, no additional risk would be anticipated.

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG/ABC/3TC FDC are as follows:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
Potential teratogenic effects of DTG/ABC/3TC; • DTG: Neural Tube Defects	The safe use of DTG/ABC/3TC in human pregnancy has not been established. DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals. 3TC and ABC, but not DTG, have been associated with findings in animal reproductive studies but have been used in human pregnancy without evidence for increased risk of teratogenicity. See the most current DTG IB for additional information [Antiretroviral Pregnancy Registry Steering Committee, 2013; Vannappagari, 2013;[GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01] There has been no association between ABC or 3TC and overall birth defects observed in the Antiretroviral Pregnancy Registry (APR), although there are some limitations to these data (http://apregistry.com/index.htm). In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A subject is eligible to continue in the study post-delivery if she is not pregnant, and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 6.5.4.8.) until at least 2 weeks after discontinuation of IP. 2. Subjects who are post-delivery and desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and be withdrawn from the study. 3. Subjects who are post-delivery are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 4. Pregnancy status is monitored at every study visit post-delivery. Pregnancies must be followed up to determine outcome (including premature termination) and status of mother and child. GSK's central safety department will also forward this information to the APR (Section 6.5.11).
Pregnancy can increase risks of HIV progression, complications and perinatal transmission	The safe use of DTG/ABC/3TC in human pregnancy has not been established. DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals. 3TC and ABC, but not DTG, have been associated with findings in animal reproductive studies.	Treatment of the underlying HIV disease. Additionally women taking ART during pregnancy can reduce risk of transmission to infant (i.e., early control of viral replication important in prevention)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
	See the most current DTG IB and approved ABC/3TC product label for additional information [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]. There has been no association between ABC or 3TC overall birth defects observed in the Antiretroviral Pregnancy Registry (APR), although there are some limitations to these data (http://apregistry.com/index.htm). Rationale described in Section 1.1 and reference is made to the HIV WHO treatment guidelines: Antiretroviral drugs are used to treat pregnant women and prevent HIV infection in infants (See Section 10 References)	It is highly recommended that the subject also establish appropriate Obstetric care or nurse/mid-wife care per local standard of care (SoC) routine management.
Mitochondrial toxicity in children with in utero/post-natal exposure to nucleoside analogues	There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues; however, these have generally involved thymidine analogues. In vitro studies assessing mtDNA depletion provided the following rank order for NRTI effects: ddC >ddI >d4T >ZDV >3TC =ABC =TDF [BIRKUS, 2002]. In addition, there is a large body of historic evidence from switch for toxicity populations, which demonstrates the advantages of switching patients on certain NRTIs, PIs or NNRTIs to ABC ±-3TC.	Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. The benefits from preventing vertical transmission of HIV infection from mother to child are considered to outweigh the risks of infants developing mitochondrial dysfunction.
Hypersensitivity (including abacavir hypersensitivity reaction [ABC HSR]) and rash	A well characterised, idiosyncratic, drug-related HSR is the most important risk associated with ABC (See Section 6.5.4.6). Exclusion of individuals found to carry the Human	Subjects positive for HLA-B*5701 were excluded from participating.in the ING117172 study Additionally, subjects with history of allergy/sensitivity to any of the study drugs

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
	Leukocyte Antigen (HLA)-B*5701 allele from ABC therapy reduces the risk of HSR. Rash, icluding Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme have been reported in patients taking ABC (See Section 6.5.4.6 and Section 6.5.4.7). HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as SJS, TEN and Erythema Multiforme were reported. Data on HSR for DTG and DTG+ABC/3TC FDC suggest that there will not be additional risk from HSR in HLA-B*5701 negative subjects receiving the DTG/ABC/3TC FDC.	are excluded (Section 4.3). Specific/detailed toxicity management guidance is provided for suspected HSR with DTG (Section 6.5.4.6) or ABC (Section 6.5.4.6), and skin reactions without systemic involvement (Section 6.5.4.7). The subject informed consent form includes information on this risk and the actions subjects should take in the event of a HSR or associated signs and symptoms. Subjects are be reminded to read the ABC HSR Warning Card accompanying their study medication and of the importance of keeping this card with them at all times.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B (HBV) virus and/or hepatitis C (HCV) virus co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries. Current treatment guidelines [DHHS, 2013; EACS, 2012] do not recommend monotheraphy with 3TC for patients	Subjects meeting the following criteria during the screening period are excluded from participating (Section 4.3). Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin). Subjects positive for HBV at screening (hepatitis B virus surface antigen positive [+HBsAg]), or with an anticipated need for HCV therapy during the study. Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
	with HBV infection, which is what subjects randomised to DTG/ABC/3TC would effectively be receiving. Additionally, discontinuation of 3TC in HBV coinfected subjects can result in severe exacerbations of HBV.	(Section 6.5.4).
Theoretical serious drug interaction with dofetilide or pilsicainide	Co-administration of DTG may increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter, resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 5.6.2).
Gastrointestinal (GI) intolerance	Non- clinical studies showed upper and lower GI toxicity, including vomiting, diarrhea and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhoea and nausea) is associated with DTG treatment in a small proportion of subjects; however there were no indications of an increased risk for peptic ulcers or serious erosions.	Routine monitoring of GI symptoms will be performed.
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. Measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV or RAL. 3TC is eliminated by renal excretion and exposure increases in patients with renal dysfunction.	Due to requirements for dose reduction of 3TC in patients with renal dysfunction, subjects with a creatinine clearance (CrCL) <50 mL/min are excluded from participating (Section 4.3). Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 6.5.4.3) and/or proteinuria (Section 6.5.4.4).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are common in HIV infected patients. The psychiatric profile for DTG (incl. suicidality, depression,	Subjects who in the investigator's judgment, poses a significant suicidality risk, will be excluded from participating in the study (Section 4.3).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
	bipolar and hypomania, anxiety and abnormal dreams) was similar or favourable compared with other ART. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared to EFV/TDF/FTC in ING114467;however, this was not duplicated in any other Phase IIb/III study conducted with DTG. See the IB for additional information.	Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour. Detailed information on subjects developing these events will be collected on designated CRF pages (Section 6.5.10).
Creatine phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 6.5.4.2).
Increased occurrence of Immune reconstitution inflammatory syndrome (IRIS)	With rapid HIV-1 RNA decline and early recovery of CD4+ cell counts there could ,theoretically, be an increase in cases of IRIS. The increased risk for HBV and HCV IRIS with DTG-containing ART is addressed above; there was a low rate of other medical conditions frequently implicated in IRIS cases. See the IB for additional information.	Subjects positive for HBsAb at screening or with active HCV illness (anticipated to require therapy) are excluded from participating. Subects will have routine laboratory monitoring.

1. Careful monitoring of events will be conducted using SAE reports and alerts for Grade 3/4 laboratory toxicities (per Division of Aquired Immunodeficiency Syndrome (DAIDS) toxicity gratings for HIV infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per Sponsor's standard Medical Monitoring practices
2. Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK) Safety Review Team (SRT) meetings. This will include in-stream review of data from this clinical trial on a regular basis; review of aggregate data on a protocol and program basis when available; and review of competitor data from the literature

1.3.2. Benefit Assessment

Pregnancy increases the risk of HIV progression whilst HIV increases the risk for maternal complications from pregnancy and poses the risk of perinatal HIV transmission to the unborn fetus. While antiretroviral treatments have significantly improved survival rates and decreased maternal-fetal transmission, earlier HIV diagnosis still remains problematic, especially in limited resource settings. Recent recommendation updates to treatment guidelines have included objectives to increase HIV screening of patients, including pregnant women (noting the importance of adopting HIV screening to be a part of prenatal care).

The 2012 WHO guidelines recommend starting all HIV-infected pregnant women on ART therapy based on CD4+ cell counts and/or WHO Stage 3 or 4 disease for life. The reduction of maternal-fetal transmission is currently being shown with the 2010 UNAIDS vision 'zero new HIV infections', and the UN General Assembly of the United Nations adoption of the 2011 Political Declaration on HIV and AIDS target to reduce the number of children infected with HIV by 2015, progress is being made toward reaching its goal of eliminating vertical transmission by 90% [United Nations General Assembly, 65th Session, Agenda Item 10, 28 March 2011]. The percentage of children newly infected today is 24% lower than in 2009 [UNAIDS, 2012] and it is expected with accelerated efforts the 90% reduction in the number of children acquiring HIV infection can be met by 2015. Global progress in HIV treatment and prevention continues to see dramatic declines in new infections among children as more pregnant women receive effective antiretroviral treatment to prevent transmission (57% today, up from 48% in 2010).

Additionally, in an examination of data from 2543 HIV-infected pregnant women participating in the Women and Infants Transmission Study (WITS), review of maternal and adverse pregnancy outcomes found that ART use according to regimen potency or class of agent was independently associated with few adverse outcomes and with a decreased odds ratio for some obstetric outcomes. Recognizing that new ART therapies must be continually reassessed, the study provides strong evidence that ART regimens used during pregnancy are not associated with major adverse maternal outcomes [Tuomala, 2005].

In conclusion, ART prevents HIV disease progression and mother-to-child transmission (MTCT) in pregnant women.

Novel effective and well tolerated drugs are needed for all sectors of the HIV population. DTG/ABC/3TC FDC is being developed as a treatment for ART- naive adult patients, and has distinct advantages over the most widely used therapies for treatment-naive patients in the following manner:

For treatment-naïve patients who initiate a regimen of 2 NRTIs plus a third antiretroviral drug, DTG/ABC/3TC offers high potency, favourable tolerability, high barrier to drug resistance, and once daily dosing. DTG/ABC/3TC is the first drug to combine all these characteristics, with demonstrated statistical superiority over Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate), which is the preferred fixed-dose

combination regimen for treatment-naïve patients, including continuation in pregnant women (DHHS guidelines, 2013; WHO, 2013).

A regimen comprised of DTG administered with ABC/3TC has been shown to be highly efficacious and well tolerated in treatment-naive subjects. In the Phase III double-blind SINGLE study (ING114467), 833 therapy-naive adults were randomized to DTG 50 mg plus ABC/3TC once daily once daily or a guidelines-preferred single tablet regimen of EFV/TDF/FTC once daily. At Week 48, the proportion with HIV-1 RNA <50 copies/mL in the DTG+ABC/3TC arm (88%) was superior to the EFV/TDF/FTC arm (81%), P=0.003. Time to viral suppression (median 28 vs. 84 days; P<0.001) and increases in CD4 cell counts (+267.1 vs. +208.2 cells/mm3; P<0.001) also favored DTG+ABC/3TC. No subjects on DTG+ABC/3TC had detectable antiviral resistance; 1 TDF-associated and 4 EFV-associated mutations were detected in EFV/TDF/FTC subjects with viral failure. In a by gender analysis, Week 48 responses in women (85%) were higher in recipients of DTG + ABC/3TC when compared to EFV/TDF/FTC (75%).

The proportion of subjects discontinuing for AEs was lower with DTG+ABC/3TC (2%) than EFV/TDF/FTC (10%); rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common on EFV/TDF/FTC, whereas insomnia was reported more frequently on DTG+ABC/3TC.

The DTG/ABC/3TC FDC thus have the potential to provide a convenient, once daily single tablet regimen, without need for a PK booster or food/fluid restrictions, and with limited safety implications resulting from theoretical or actual drug: drug interactions compared to other antiretroviral agents (including EFV and those requiring a PK booster).

1.3.3. Overall Benefit:Risk Conclusion

Based on animal data, DTG is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans. Both ABC and 3TC have been studied during pregnancy (See Section 1.1), pregnancy outcomes from these studies are monitored through the ARV Pregnancy Registry (APR). In summary, taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with DTG/ABC/3TC FDC are justified by the anticipated benefits that may be afforded to pregnant women with HIV infection (decreased disease progression due to maintenance of suppression) and their unborn children (reduction in HIV transmission).

2. OBJECTIVE(S)

Objective(s)

Primary

Mother:

- To describe the total plasma DTG PK parameters with the DTG/ABC/3TC FDC during Weeks 18-26, Weeks 30 – 36 of the third trimester of the pregnancy and 8-12 weeks postpartum;
- To further characterize the safety and tolerability of DTG/ABC/3TC FDC when used during pregnancy.

Secondary

Mother:

- To assess the antiviral activity of the DTG/ABC/3TC FDC when administered during pregnancy;
- To assess the immunologic activity of DTG/ABC/3TC FDC;
- To assess the incidence of treatment-emergent genotypic and phenotypic resistance in subjects who meet confirmed virologic withdrawal criteria;
- To evaluate the unbound DTG concentrations in plasma during Weeks 18-26 and Weeks 30-36 of the pregnancy and 8-12 weeks postpartum;
- To compare the DTG concentrations in plasma from cord blood with those in maternal plasma at the time of delivery;
- To characterize birth outcomes;
- To characterize pregnancy outcomes.

Infant:

- To characterize infant outcomes at birth;

3. INVESTIGATIONAL PLAN

3.1. Study Design

ING200336 is a single arm open-label interventional study for women who become pregnant while participating in ING117172. It is interventional in design with the goal to evaluate DTG PK and safety in pregnancy during treatment with DTG 50 mg/ABC 600 mg/3TC 300 mg FDC once daily. Eligible subjects are HIV-1 infected women participating in study ING117172 who become pregnant and are required to be withdrawn. The ING200336 study is being offered only to those women

who were on the DTG/ABC/3TC FDC treatment arm. **Note**: While the WHO's treatment guidance recommends that women who are on ART at the time they become pregnant continue such therapy if they are responding to that ARV treatment, it's important that the investigator refer to local country guidelines with regards to recommendations on selection (or switching) of ARVs when the pregnancy is identified; treatment should minimally reflect that of local standard of care. The number of women that will be enrolled into this protocol cannot be established *a priori*, as unintended pregnancies cannot be determined in advance (See Section 4.1 for further details).

Subjects will continue to receive DTG/ABC/3TC FDC once daily after completion of the primary and secondary assessments. The primary outcome analyses will take place after the last subject enrolled gives birth. As this study will remain open until ING117172 is closed, analyses of data may be conducted in this open label study prior to this timepoint as required by the Sponsor (e.g., when an adequate number of subjects with PK data are available, for regulatory filings).

Given the requirement that subjects who become pregnant on ING117172 be withdrawn, sites who are interested in enrolling pregnant women from ING117172 onto ING200336 should seek IRB/EC approval for ING200336 in advance of identifying such subjects, in order that DTG/ABC/3TC FDC treatment may be continued without interruption.

Screening Period

Subjects will participate in a short screening period which includes an assessment for potential pregnancy complications (e.g., hypertension, diabetes, and underlying infections) and a thorough obstetric history (including gravidity, previous complications and/or risks, etc.) at Screening or up through Day 1. Any subject who became pregnant but meets virologic withdrawal criteria on ING117172 will not be eligible to participate in this study. The subject must also establish appropriate obstetric care per local SoC. It will be necessary for the subject to be willing to share medical information, as necessary, to the HIV investigator for both herself and her infant to facilitate collection of delivery, birth and infant outcomes by the investigator. Once the subject learns she is pregnant, there are two scenarios for enrollment:

1. If the subject wants to enter the pregnancy study, and has been seen within 28 days for a regularly scheduled ING117172 visit, the site would schedule a Withdrawal visit, which still must remain within the 28 day window of the visit when pregnancy was documented. The previous visit results will be used as the "screening visit" to qualify the subject for enrollment and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336. A urine pregnancy test, as well as a urine dipstick to monitor protein, must be performed on Day 1.
2. If the subject is determined to be pregnant outside of a study visit and wants to enter ING200336 but has not been seen within the 28 day window, the site is to perform an unscheduled ING117172 visit to collect adverse events/serious adverse events (AEs/SAEs), plasma HIV-1 RNA and laboratory results, including a serum pregnancy test, as well as a urine dipstick to monitor protein, in order to document the subject's current medical status. If the pregnancy is confirmed, the site would then schedule

the Withdrawal visit within 28 days of the unscheduled visit. The unscheduled visit results will be used to qualify the subject for enrollment (i.e., is the screening visit) and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336.

3. In both scenarios the Withdrawal visit for ING117172 will also be Day 1 for ING200336 to ensure no disruption in provision of study treatment. In the event the subject miscarries or electively terminates the pregnancy prior to Day 1 (Baseline) of ING200336, she must still be discontinued from ING117172 and followed per the requirements of ING117172, and may not continue enrollment into study ING200336.

In both of these scenarios new demographic, Baseline characteristics, concomitant medications, medical history and HIV associated conditions will be collected on Day 1, as well as a thorough maternal history which includes an assessment for pregnancy risks (e.g., live births, still births, elective terminations, previous miscarriage, pre-term labor (before Week 37) preterm birth, preeclampsia, low amniotic fluid (oligohydramnios), gestational diabetes, ectopic pregnancy, placenta previa or abruption, drug induced hepatitis, poor weight gain, anemia, poor nutrition, and an incompetent cervix.) and any previous pregnancy history (including gravidity). If the subject provided consent and a PGx sample was collected in study ING117172, there will be no requirement to take another PGx sample (the original sample will linked to the ING117172 subject treatment numbers in both studies. If the subject consented, but no PGx sample was drawn while participating in ING117172, a new consent will be provided for ING200336 and a PGx sample will be drawn in this study (if the subject consents to participate).

If there is an ongoing, unresolved AE and/or SAE at the time of the Withdrawal visit in ING117172 the AE/SAE will be followed for event outcome, which will be recorded in the eCRF, as part of ING117172 (i.e., followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up). The AE/SAE will be transcribed as medical history in ING200336. Any exacerbation or worsening of the AEs and/or SAEs from ING117172 during subject participation in ING200336, will be recorded as a new entry in the AE or SAE eCRF pages for ING200336 with a start date reflecting the clinical worsening, and will not be recorded for ING117172. All SAEs (including those 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 or ViiV concomitant medication) and any non serious AEs of special interest (defined in the study procedure manual) occurring from the withdrawal visit in ING117172 through to administration of IP at Day 1 of ING200336, will be recorded in the eCRF for ING117172.

All AEs and SAEs occurring from Day 1 in ING200336 through to the follow up contact will be collected and recorded in the eCRF for ING200336, regardless of relationship to study participation or any other causality.

Pregnancy Period and Delivery

Please note: The HIV provider is responsible for HIV care and will collaborate and share information with the subject's obstetric care provider, discuss the subject's participation

in this study, the necessary procedures at delivery, to share HIV information, and to collect birth and infant outcomes from the subject's obstetric care provider and/or the pediatric health provider for the infant.

Mothers:

After all Withdrawal procedures for ING117172 have been completed and results are available and documented, subjects who sign informed consent and fulfil eligibility requirements may be enrolled in ING200336. Subjects will begin Day 1 and continue to receive DTG/ABC/3TC FDC treatment in an open-label fashion of ING200336.

All subjects will have serial PK sampling while on study, one during Weeks 18 - 26, one during Wks 30-36 and one at 8-12 weeks postpartum. Serial plasma samples will be collected during each PK visit for the determination of DTG (total and unbound) concentrations. Samples will be collected prior to dosing and at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. Subjects should be reminded prior to their PK visit that they will need to come to the site two days in a row in order to complete the 24 hour PK sampling and that no doses can be missed during the 3 days prior to the scheduled PK visit. Instructions regarding the PK visit can be found in the Study Procedures Manual (SPM). A plasma HIV-1 RNA and CD4+ cell count sample will be drawn within 24 hours of delivery and on the day of the post-partum PK evaluation. At delivery, if feasible, a cord blood and a time-match maternal blood sample will be collected to evaluate DTG/ABC/3TC FDC concentrations in plasma.

HIV-1 RNA, CD4+ cell counts, and laboratory testing will be conducted at each visit (see Time and Events Table in Section 6.1).

Pregnancy related complications and diagnoses will be captured as AEs and SAEs as outlined in Section 6.5.5.

Following Day 1, no changes or intensification of the ART regimen will be permitted, except the additional use of ZDV as required at delivery (e.g., per local guidelines). Note: **Nevirapine (NVP) may not be used** in lieu of ZDV for peripartum prophylaxis. Nevirapine could significantly decrease the levels of DTG due to enzyme induction and result in PK variability (See Section 5.6.2).

Medications other than DTG/ABC/3TC FDC will not be provided by the study. It is recommended the subject begin prenatal multivitamins and folate supplementation early in the pregnancy as per local guidelines (See Section 5.6.1 and Section 5.6.2, Permitted and Prohibited Concomitant Meds); appropriate prophylaxis for opportunistic infections, as well as vaccinations, should be coordinated and/or administered as guided by local SoC. It will be necessary for the subject to be willing to share medical information for both herself and her infant from her obstetric care provider to facilitate collection of delivery, birth and infant outcomes by the investigator.

Please note: In the event of a spontaneous loss of pregnancy during the study, pregnancy outcomes are collected in the eCRF "Delivery Visit". After the loss is confirmed the subject may continue to receive DTG/ABC/3TC FDC unless they meet the criteria for confirmed virologic withdrawal. They may continue to receive DTG/ABC/3TC FDC

after completion of the primary and secondary assessments (in which case they will be followed q12 weeks) until study medications are locally approved and commercially available or until they no longer receive benefit. In this case the subject must agree to use contraception to avoid a 'new' pregnancy (See Section 6.5.4.8).

Infants: At delivery, it will be necessary for the HIV investigator to contact the subject's obstetric care and pediatric health provider for the infant to obtain information about the newborn examination. Data collection of infant outcomes includes gestational age, birth weight, length and head circumference at the 8-12 week post-partum visit measurements, Apgar scores (at 1 and 5 minutes), whether the infant is small, appropriate or large for gestational age [SGA, AGA, or LGA], intrauterine growth restriction [IUGR], birth defects and the presence or absence of major congenital abnormalities to be recorded in the CRF. Details of the CBC with differential assessment on or after the first day of life and any chemistry assessment on or after 1 day of life, if standard of care, should also be collected and recorded in the CRF by the HIV provider (see Section 6.5). HIV status of the infant, if known, should also be recorded in the CRF.

Newborn ARV prophylaxis treatment as per local country guidelines should still be followed by the pediatric health provider. An international APR has been established to track pregnancy-related AEs and fetal outcomes. Pregnancy outcomes and status of the mother and fetus/child will be reported by the ING200336 investigator to GSK who will report information collected to the APR.

Study Completion

Subjects are considered to have completed the study after completing the postpartum evaluation approximately 8-12 weeks post delivery.

Continuation Phase

Women may continue to receive DTG/ABC/3TC FDC after completion of the primary and secondary assessments until study medications are locally approved and commercially available or until they no longer receive benefit, the subject meets a protocol-defined reason for discontinuation or development of DTG/ABC/3TC is terminated. During this time, subjects will be monitored every 12 weeks to ensure they continue to derive clinical benefit from DTG/ABC/3TC FDC. Note: the duration of the study completion will vary from country to country and is dependent on the recruitment time for the study and the time taken to achieve local approval and availability for marketing.

Should the subject become pregnant during the Continuation phase, she must be withdrawn from the study and transitioned to the commercial supply of components DTG and ABC/3TC or DTG/ABC/3TC FDC if available.

Follow-up

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a follow-up (FU) visit approximately four weeks after their last visit. Assessments at the

FU visit should reflect any ongoing complaints (e.g., blood draws to follow any clinically significant laboratory abnormality). The FU visit is not required for successful completion of the study.

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 (Section 6.1), are essential and required for study conduct.

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. Discussion of Design

One of the primary study objectives is to characterize the PK of DTG (total and unbound) in pregnant HIV-infected women using DTG/ABC/3TC FDC. A longitudinal design is used in this study with PK evaluations based on intensive PK sampling to be performed serially during pregnancy as well as postpartum in each of subjects to be enrolled. As the changes in PK during pregnancy are most prominent in the third trimester, the study will evaluate the steady-state PK of DTG during the 2nd and 3rd trimester compared to that observed at 8-12 weeks postpartum. The design allows each woman to serve as her own control to evaluate the significance of change in DTG PK during pregnancy comparison versus the non-pregnant state (postpartum).

As DTG is a drug with low apparent clearance (CL/F) and high protein binding; its PK, especially unbound concentration in plasma is sensitive to plasma protein level. As a reduction in plasma protein is often observed during pregnancy, the impact of pregnancy on unbound DTG concentration is also evaluated in this study.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

This is an open-label study. The number of women that will be enrolled into this protocol cannot be established *a priori*, as unintended pregnancies cannot be determined in advance. The maximum number of women would include all of those women randomized to DTG/ABC/3TC FDC (n~237), though unintended pregnancies in all of these women would not be anticipated. Based on pregnancy rates from 2 recent DTG studies, the anticipated rate of unintended pregnancy over 48 weeks would be approximately ~5% (n~12). Should 12 subjects enroll, this would likely be sufficient to obtain at least 8 subjects providing evaluable DTG PK parameters in the third trimester and postpartum.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the IP or other study treatment that may impact subject eligibility is provided in the most current version of the DTG IB, IB supplements, product labels, and/or local prescribing information.

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.

Subjects eligible for enrolment in the study must meet all of the following 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).**

Eligible subjects must

- be able to understand and comply with protocol requirements, instructions, and restrictions;
- be likely to complete the study as planned;
- be considered an appropriate candidate for participation in an investigative clinical trial with oral medication (e.g. no active substance abuse, acute major organ, disease, or planned long term work assignments out of the country, etc.).

Subjects eligible for enrolment in the study must meet all of the following criteria unless stated otherwise:

1. HIV infected females participating in ING117172 on the DTG/ABC/3TC treatment arm who became pregnant with a singleton and have not met any safety or confirmed virologic withdrawal criteria;

2. Signed and dated written informed consent is obtained from the subject or the subject's legal representative prior to screening;

3. Willingness and intent to continue pregnancy;

4. Willingness to continue to receive DTG/ABC/3TC FDC;

5. Willingness to enter the Antiretroviral Pregnancy Registry;

6. Willingness to share medical information about herself and her infant for collection of delivery and infant outcomes as it relates to this study;

7. **Subjects enrolled 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. History of allergy/sensitivity to DTG, ABC and/or 3TC;

2. History of severe preeclampsia, eclampsia, or HELLP;

3. Any evidence of an active Center for Disease Control and Prevention (CDC) Category C disease [CDC, 1993], except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200cells/mm3;

4. Subjects with any degree of hepatic impairment;

5. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject;

6. Subjects who in the investigator's judgment, poses a significant suicidality risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk;

7. Subjects with evidence of ongoing hepatitis B infection at screening, or anticipated need for HCV therapy during the study.

Exclusionary Treatments prior to Screening or Day 1

8. Treatment with any of the following agents within 28 days of Baseline: radiation therapy; cytotoxic chemotherapeutic agents; any immunomodulators that alter immune responses.

9. ***Subjects enrolled in France:*** the subject has participated in any study, other than ING117172, using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

Exclusionary Laboratory Values or Clinical Assessments at Screening

10. Any verified Grade 4 laboratory abnormality with the exception of Grade 4 lipid abnormalities (total cholesterol, triglycerides, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol). A single repeat test is allowed during the Screening period to verify a result.

11. Any acute laboratory abnormality observed in ING117172 or in any Screening laboratory assessments for ING200336, which, in the opinion of the Investigator, would preclude the subject's participation in the study;

12. Hyperbilirubinemia of unknown etiology;

13. Confirmed (with no more than 1 repeat evaluation) Grade ≥ 2 urine protein (dipstick), serum creatinine, total bilirubin, ALT or AST at the time of the screening lab;

14. Subject has CrCL of <50 mL/min via Cockroft-Gault method at the time of the screening visit.

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. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the DTG 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 IPs.

4.5. Withdrawal Criteria

Subjects permanently discontinuing study treatments prior to the 8-12 week post-partum visit are considered to be withdrawn from the study treatment and also from the study. Similarly, subjects who enter the Continuation Phase but permanently discontinue participation in the Continuation Phase prior to local commercially available DTG/ABC/3TC FDC, 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 **may** be prematurely discontinued from the study for any of the following reasons:

- Subject or Investigator noncompliance;
- At the request of the subject, Investigator, or Sponsor;
- The subject requires concurrent prohibited medications during the course of the study. The subject may remain in the study if in the opinion of the Investigator and the medical monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject.

Subjects **must** be prematurely discontinued from the study for any of the following reasons:

- The subject refuses further treatment and/or follow-up evaluations and decides to discontinue participation or is lost to follow-up;
- It is determined at any time during the study that the subject is pregnant with more than one baby;
- Continued participation in the study would be detrimental to the subject's or baby's health or well-being;
- Subject requires substitution or dose adjustment of DTG, ABC or 3TC;
- Liver toxicity where stopping criteria specified in Section 6.5.4 are met and no compelling alternate cause is identified;
- Virologic withdrawal criterion as specified in Section 4.5.1 are met;
- Grade 4 clinical AE considered causally related to IP;
- Renal toxicity where specified in Section 6.5.4.3 are met and no compelling alternate cause is identified;
- Clinically suspected ABC HSR as described in the Section 6.5.4.6.
- Rash toxicity as specified in Section 6.5.4.7 is met and no compelling alternate cause is identified;
- A new pregnancy during the Continuation Phase as described in Section 3.1. As a reminder, subjects who are post-delivery and desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

If a subject is prematurely or permanently withdrawn from the study, perform the procedures described in the Time and Events Table (Section 6.1) for the Withdrawal and Follow Up visits. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study. Subjects with on-going clinical or clinically significant laboratory AEs at the time of Withdrawal should return for the Follow-up visit.

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 (e.g., via telephone calls and/or sending 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 he/she will 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. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the eCRF. Every effort should be made by the Investigator to follow up subjects who withdraw from the study. In the event that a subject is prematurely discontinued from the study at any time due to an AE (see Section 6.5.5), the procedures stated must be followed. Subjects who are withdrawn from the study will not be replaced.

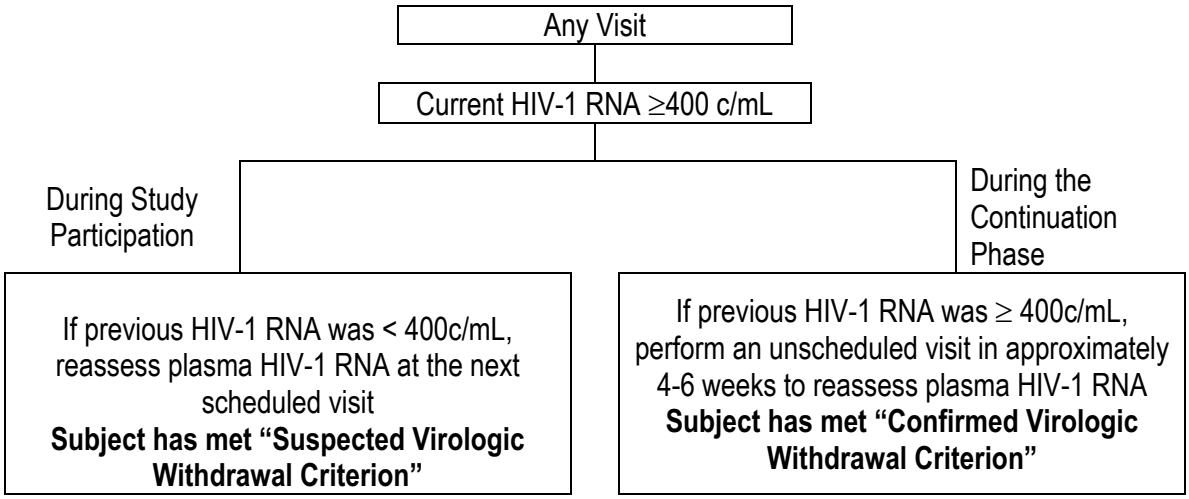
Subjects may have a temporary interruption to their study treatment for management of toxicities (Section 6.5.2).

4.5.1. Virologic Criteria for Subject Management and Viral Resistance

For the purpose of clinical management in this study, subjects with plasma HIV-1 RNA levels >400 c/mL at any time point must have HIV-1 levels reassessed using the algorithms below (Figure 1) which details protocol defined clinical management for subjects who have met a **"suspected or confirmed virologic withdrawal criterion"**. Investigators should not schedule reassessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Subjects should have received full doses of DTG/ABC/3TC FDC for at least 2 weeks at the time of HIV-1 RNA reassessment for any HIV-1 RNA level >400 c/mL.

Virologic Criteria for Subject Management

Figure 1 Virologic Criteria for Subject Management



If HIV-1 RNA level remains ≥400 c/mL, a plasma for storage sample from the "suspected virologic withdrawal criterion" visit will be used for HIV-1

genotype/phenotype testing. Subjects may continue to receive IP at the discretion of the Investigator until results of resistance testing are available at which time the subject must be discontinued from the study. If a subject is prematurely discontinued from the study, the Investigator must make every effort to perform the evaluations outlined in the Time and Events Table. These data will be recorded as they comprise essential evaluations needed to be done before discharging any subject from the study.

Note: Plasma samples with <400 c/mL of HIV-1 RNA will not be analyzed, as the protease/reverse transcriptase/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <400 c/mL

4.6. Screening Failures

A subject is considered a screen failure if after providing informed consent, the subject's circumstances or conditions change or the outcome of a test or assessment becomes available which results in the subject's failure to meet one or more of the entry criteria, or results in the investigator deciding that the subject is no longer an appropriate study candidate.

A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility.

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

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

This study has an open-label design. The dolutegravir 50 mg /abacavir 600 mg /lamivudine 300 mg FDC tablet is defined as the IP throughout this study and will be provided by GSK. All other ART (i.e., ARVs given to the subject during delivery as per SOC) is not considered to be IP and is not provided by GSK. **Note: Nevirapine (NVP) may not be used** in lieu of ZDV during delivery. NVP could significantly decrease the levels of DTG due to enzyme induction and result in PK variability (See Section 5.6.2).The contents of the label 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. 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 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the

investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Note: Newborn ARV prophylaxis treatment as per SoC should be recommended to the obstetric and/or pediatric care provider, however, is not considered to be IP and is not provided by GSK.

5.1.1. Tablet Formulation of DTG/ABC/3TC

The dolutegravir 50 mg /abacavir 600 mg /lamivudine 300 mg FDC tablet is a purple, oval, biconvex tablets debossed with '572 Tri' on one side and plain on the other side. The tablet contains 52.6 mg DTG sodium which is equivalent to 50 mg DTG free acid, 702 mg ABC sulphate which is equivalent to 600 mg ABC and 300 mg 3TC. The tablets are packaged into high density polyethylene (HDPE) bottles with child-resistant closures that include induction seals. The bottles contain a desiccant. Tablets **must be** stored in the original package with the bottle tightly closed. Desiccants must be kept in the bottle to protect from moisture.

5.2. Treatment Assignment

Subjects will initiate therapy with DTG/ABC/3TC FDC following confirmation of fulfilment of study entry criteria. A unique treatment number will be assigned for each subject participating in the study. Subjects who are enrolled into the trial and subsequently withdrawn may not be re-screened.

5.2.1. Dosage and Administration

This is an open-label study. All subjects will be administered DTG 50 mg/ABC 600 mg/3TC 300 mg FDC tablet administered once daily, with or without food.

5.3. Blinding

NA, this is an open-label study.

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 IP 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. This assessment will be conducted each time the subject receives a new (refill) supply of study medication

through the Withdrawal visit or study completion. These data will be recorded in the subject's CRF, but will not be summarized for analysis purposes.

5.6. Concomitant Medications and Non-Drug Therapies

Subjects should 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. All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that the drug name and the dates of administration are to be recorded.

5.6.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 5.6.2) or those routinely used as local standard of care (e.g., IV Zidovudine during delivery). 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 CRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma 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 HIV-1 plasma RNA at the next scheduled assessment.

DTG/ABC/3TC FDC should be administered 2 hours before or 6 hours after taking antacid products or sucralfate containing divalent cations (e.g. aluminium and magnesium). Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable.

DTG/ABC/3TC FDC can be co-administered with calcium or iron supplements if taken with a meal. Under fasted conditions, DTG/ABC/3TC FDC should be given 2hr prior to OR 6 hr after calcium or iron supplements

Metformin concentrations may be increased by DTG. Subjects should be monitored during therapy and a metformin dose adjustment may be required.

5.6.2. Prohibited Medications and Non-Drug Therapies

HIV immunotherapeutic vaccines are not permitted at any time during the study (see Section 5.6.1 for guidance regarding non-HIV vaccines). Other experimental agents, antiretroviral drugs, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria, Section 4.3). Systemically administered immunomodulators that directly affect immune responses are prohibited. HCV therapy during study will not be permitted as approved HCV therapies at present include interferon.

For a detailed list of prohibited medications, please consult the SPM.

5.6.2.1. Prohibited medications for subjects taking DTG/ABC/3TC FDC

The following medications or their equivalents must not be administered concurrently with DTG/ABC/3TC FDC due to induction of UGT1A1 and/or CYP3A4 leading to the potential for reduction in dolutegravir levels.

- barbiturates
- carbamazepine
- oxcarbazepine
- phenobarbital
- phenytoin
- rifampin/rifapentine
- St. John's wort
- dofetilide

Dofetilide is prohibited, as the DTG component of DTG/ABC/3TC FDC may inhibit their renal tubular secretion, resulting in increased dofetilide concentrations and potential for toxicity.

Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided; however, short treatment courses (for example, 30 days or less), replacement therapy (e.g., for Addison's Disease) and topical, inhaled, or intranasal use of glucocorticosteroids 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.

Acetaminophen is not to be used in patients with acute viral hepatitis.

5.7. 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.

Continuation Phase

Women will be given the opportunity to continue to receive DTG/ABC/3TC FDC after study completion (in which case they will be followed every 12 weeks) until one of the following occurs:

- DTG/ABC/3TC FDC is locally approved and commercially available,

- The subject no longer derives clinical benefit from DTG/ABC/3TC FDC,
- The subject meets a protocol-defined reason for discontinuation or
- The development of DTG/ABC/3TC FDC is discontinued.

See Section 3.1, Study Completion, for complete details.

Note: Should the subject become pregnant during the Continuation phase, she must be withdrawn from the study and transitioned to the commercial supply of components DTG and ABC/3TC or DTG/ABC/3TC FDC if available.

5.8. Treatment of Study Treatment Overdose

For this study any tablet intake exceeding the randomized daily number of tablets for IP will be considered an overdose.

For the purposes of this study, an overdose is not an AE (Refer to Section 6.5.5.1) 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 6.5.5.2.

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

The Investigator should use clinical judgment and also refer to the prescribing information for approved ARTs, as appropriate in treating overdose, as GSK is unable to recommend specific treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 4 Time and Events Table

Procedures	Screen*, **	Day 1	Ante partum	Delivery	Post-Partum	Continuation Phase	Withdrawal	Follow-up[14]
			Monthly – every 4 weeks		8-12 weeks post delivery	Every 12 weeks after Post Partum Visit		
Written Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Subject Demography	X							
Medical History[1]		X			X	X		
Concurrent medical conditions		X						
CDC HIV-1 classification		X						
HIV-associated conditions			X	X	X	X	X	X
Cardiovascular risk assessment[2]	*							
Prior Art history	*							
Gravidity Maternal history		X						
Pregnancy risk assessment	X	X	X					
Uteroplacental Outcomes at Delivery[3]				X				
Infant Outcomes[4]				X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X
Limited Physical Examination[5]		X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

Procedures	Screen*, **	Day 1	Ante partum	Delivery	Post-Partum	Continuation Phase	Withdrawal	Follow-up[14]
			Monthly – every 4 weeks		8-12 weeks post delivery	Every 12 weeks after Post Partum Visit		
Serious Adverse Events[6]	X	X	X	X[5]	X	X	X	X
Pharmacokinetic Sampling[7]			X[6]	X	X			
Cord & maternal blood sample[8]				X				
Columbia Suicidality Severity Rating Scale[9]		X	X		X	X	X	
Laboratory Assessments								
Pregnancy Assessment[15]		X			X	X		
Hematology	**	**	X		X	X	X	X
Clinical Chemistry	**	**	X		X	X	X	X
Urinalysis. Including dipstick for protein analysis	**		X		X	X		X
Quantitative plasma HIV-1 RNA[10]	**	**	X	X	X	X	X	
Lymphocyte subsets	**	**	X	X[5]	X	X		X
PGx Sampling[11]		X						
Plasma for storage[12]	X	X	X	X	X	X	X	X
Dispense IP		X	X	X	X	X[13]		

*Baseline information, including cardiovascular risk and prior ART therapy will be transferred from ING117172 to serve as baseline/screening data in this study.

**HIV-1 RNA, lymphocyte subset, and laboratory assessment (hematology, chemistry, and urinalysis including a dipstick) data collected at the ING117172 unscheduled or last visit within 28 days of learning of the pregnancy will be transferred to serve as screening data in this study. The ING117172 Withdrawal visit will serve as the ING200336 Day 1. Gravidity: Maternal history and pregnancy risk assessment may occur at either Screening or Day 1 visit.

1. Medical History includes any changes in smoking status
2. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions and will have previously been collected in ING117172
3. Assessment of pregnancy outcomes (e.g., spontaneous losses, induced abortions, still births, pre-term births, preeclampsia)
4. Assessment of maternal and infant outcomes, including live births, gestational age, presence or absence of major congenital abnormalities, and infant height, weight, [including percentiles, SGA, AGA, LGA, IUGR], head circumference, and presence or absence of major congenital abnormalities) at birth (See Section 6.4.1). If known, HIV status of the infant will be collected at the 8-12 week post-partum visit.
5. Limited physical examination to include blood pressure at Baseline (recorded in eCRF), heart rate and weight at each visit (recorded in eCRF at Baseline and on lab requisition at all visits) for determination of CrCL. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
6. From the time a subject consents to participate in ING200336 and administration of IP at Day 1, only 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 in the eCRF for ING200336. Only SAEs related to study participation or to a concomitantly administered GSK or ViiV product will be collected between obtaining informed consent and administration of IP at Day 1.
   Note: At the time of the Withdrawal visit in ING117172 if there is an ongoing, unresolved adverse event (AE) and/or serious adverse event (SAE) it will be left in ING117172 as unresolved and transcribed as medical history in ING200336. If the AE and/or SAE worsen after enrollment into ING200336 it will be recorded on the AE/SAE forms in ING200336.
7. Intensive PK visit: The PK evaluations should be scheduled for study visits at Weeks 18-26, Weeks 30-36 and 8-12 weeks postpartum. The DTG dose on serial PK sampling days is to be given with a light meal/snack PK should be scheduled so that witnessed dosing of DTG/ABC/3TC FDC is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing.The PK visit should be re-scheduled if the subject took their morning dose prior to coming into the clinic on the PK sampling day. See SPM for additional details.
8. If feasible, a cord and maternal blood sample will also be collected at delivery and if possible within 30 minutes of each other.
9. Suicidality Questionnaire will be conducted q 12 weeks during the Continuation Phase.
10. HIV-1 RNA and lymphocyte to be drawn within 24 hours of delivery and on the day of the post-partum PK evaluation.
11. The PGx sample should be collected at Day 1 if not collected during participation in ING117172, however this sample may be collected at any time during the study.
12. Plasma samples for storage will be collected at each visit for possible future analyses (including but not limited to HIV-1 RNA genotypic and phenotypic analyses in confirmed cases of subject withdrawal, HIV-1 RNA levels, when samples are lost or arrive at the laboratory unevaluable, and immunological parameters; see Section 6.5.3)
13. Only for subjects who continue DTG/ABC/3TC and are seen in the clinic every 12 weeks until DTG/ABC/3TC is commercially available locally. Note: after delivery, subjects must use one of the contraception methods to avoid a 'new' pregnancy
14. A Follow up visit may be conducted approximately 4 weeks after the last dose of study provided IP, and is required only if the subject has ongoing SAEs or non-serious AEs (as outlined in the SPM) at the last on study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
15. Serum pregnancy tests will be performed at the Post-Partum and Continuation Phase visits. Remind subjects who are post-delivery of the need to avoid pregnancy while in the study and adherence to the study's contraception requirements.

6.1. Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or her legal representative) 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/Independent 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.

Eligibility criteria must be carefully assessed at the Screening and Day 1 visits. Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the CRF.

6.1.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events Table (Section 6.1). Subjects will participate in a minimal screening period which includes an assessment for potential pregnancy complications (e.g., hypertension, diabetes, etc.) and a thorough obstetric history (including gravidity, previous complications and/or risks, etc.). Any subject meeting safety, virologic withdrawal and/or withdrawal criteria on ING117172 will not be eligible to participate in this study.

Once the subject learns she is pregnant, there are two scenarios for enrollment:

1. If the subject is determined to be pregnant, wants to enter ING200336, and has been seen within 28 days for a regularly scheduled ING117172 visit, the site would perform an ING117172 Withdrawal visit, which still must remain within the 28 day window of the visit when pregnancy was documented. The previous visit results will be used as the "screening visit" to qualify the subject for enrollment and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336. A urine pregnancy test and a urine dipstick to evaluate protein must be performed on Day 1.
2. If the subject is determined to be pregnant and wants to enter ING200336 but has not been seen within 28 days for a regularly scheduled ING11712 visit, the site is to perform an unscheduled ING117172 visit to collect adverse events/serious adverse events (AEs/SAEs), plasma HIV-1 RNA and laboratory results, including a serum pregnancy test and a urine dipstick to evaluate protein, in order to document the subject's current medical status. If the pregnancy is confirmed, the site must perform an ING117172 Withdrawal visit within 28 days of the unscheduled visit. The unscheduled visit results will be used to qualify the subject for enrollment (i.e., is the screening visit) and the Withdrawal visit is used for the Baseline (Day 1) visit (with verification that the subject still meets all entry criteria) for ING200336.

In both scenarios the Withdrawal visit for ING117172 will also be Day 1 for ING200336 to assure no disruption in provision of study treatment. In the event the subject miscarries or electively terminates the pregnancy prior to Day 1 (Baseline) of ING200336, she must still be discontinued from ING117172 and followed per the requirements of ING117172 and may not continue enrollment into study ING200336.

In both of these scenarios, new demographic, Baseline characteristics, concomintant medications (other than previous ARVs), medical history and HIV associated conditions will be collected on Day 1, as well as an obstetric history. If the subject provided consent and a PGx sample was collected in study ING117172, there will be no requirement to take another PGx sample (the original sample will be linked to the ING117172 subject ID's in both studies.). If the subject consented, but no PGx sample was drawn while participating in ING117172 a new consent will be provided for ING200336 and a PGx sample will be drawn in this study.

At the time of the Withdrawal visit in ING117172 if there is an ongoing, unresolved adverse event (AE) and/or serious adverse event (SAE) it will be left in ING117172 as unresolved and transcribed as medical history in ING200336. If the AE and/or SAE worsen after enrollment into ING200336 it will be recorded on the AE/SAE forms in ING200336.

6.2. Pharmacokinetics

Samples for determination of DTG concentrations in plasma (total and unbound) and cord plasma (total) will be collected in the study.

6.2.1. Pharmacokinetic Endpoints

Primary PK endpoints

DTG AUC (0-τ) , C_{max}, C_{τ}, CL/F, Vss/F, and t½ based on intensive PK sampling during the second and third trimesters of pregnancy (Weeks 18-26 and 30-36) and at 8-12 weeks postpartum.

Secondary PK endpoints

- Tmax and C0 based on intensive PK sampling during the third trimester of pregnancy and at 8-12 weeks postpartum
- C0 and Tmax based on intensive PK sampling during the second and third trimesters of pregnancy (Weeks 18-26 and 30-36) and at 8-12 weeks postpartum
- Unbound DTG concentrations in plasma at 3 and 24 hours post dose at the PK visits during the second and third trimesters and at 8-12 weeks postpartum
- Total DTG concentrations in plasma from cord blood compared to those in maternal plasma at the time of delivery.

6.2.2. PK Sample Collection

Blood samples (2 mL each except for the 3-hour and 24-hour post dose samples which require 6 mL samples) for evaluation of total DTG plasma concentrations will be collected during study visits within Wks 18-26 and Wks 30-36 of pregnancy, and at 8-12 weeks post partum. At each PK visit, samples will be collected prior to dosing and at 1, 2, 3, 4, 6, 8, 12 and 24 hours post dosing. The pre-dose sample should be collected within 15 minutes prior to the dose on the day of PK visit. Subjects should be reminded prior to their PK visit that:

1. she will need to come to the site two days in a row in order to complete the 24 hour PK sampling;
2. no doses can be missed during the 3 days prior to the scheduled PK visit;
3. she should not take the dose at home on the PK day as the dose will be taken at the site under supervision after the pre-dose sample is collected;
4. she should switch to morning dosing at least 3 days prior to the PK visit if she usually takes the dose at night.

Instructions regarding the PK visit can be found in the SPM.

At delivery: If feasible, a cord and maternal blood sample will also be collected at delivery and if possible within 30 minutes of each other. **Note:** at time of delivery, witnessed dosing of DTG/ABC/3TC FDC prior to delivery must occur and the time of previous dose taken must be collected. .

Plasma will be extracted from the blood samples collected and shipped to GSK or its designee for determination of DTG plasma concentrations (total and unbound) by a validated LC/MS/MS assay.

Important Information on collection of PK samples

Please refer to the SPM for PK sample collection, processing, and shipping instructions. The actual date and time of each PK sample collection will be recorded in the eCRF. In addition, to enhance the quality of PK data collection, subjects will be asked to complete a dosing card for the three doses prior to each PK visit (with the exception of PK sampling at delivery), with the following information which will be recorded in the eCRF.

- Actual date and time of dosing.
- Whether or not the subject vomited within 4 hours of dosing (this applies only to the dose taken immediately prior to the PK visit).
- The dosing information recorded in the eCRF will be derived from dosing cards that are provided to the subjects. If the dosing card is missing, blank, or incomplete, obtain the missing information by oral interview by site personnel and retain in source documents.

Site personnel will contact each subject prior to the PK visit to remind and inform subjects of the following:

- When their next visit is scheduled, time to arrive at the site and any other practical information and instructions with regard to the PK sampling;
- To complete all sections of the dosing card before the visit;
- Study drug will be administered at the study site at the PK visits; subjects should NOT take their DTG/ABC/3TC FDC dose prior to coming to the site.

On the days of the PK sampling visits (other than at Delivery):

- Review dosing cards and obtain missing information by oral interview and retain in source documents, as appropriate. If a subject presents at the clinic for PK sample collection having already taken the morning dose the PK sample should not be collected as planned and the study visit should be rescheduled. If the subject has not taken the morning dose but has missed one of the previous three doses, collect as much information as possible and continue with PK sample collection.
- Administer study drug and record date and time of dosing and if subject vomits within 4 hours of dosing.

6.3. Efficacy

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 6.1). 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 LLOD for a given assay) additional exploratory methods may be used to further characterize HIV-1 RNA levels.

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ lymphocyte counts according to Time and Events schedule (Section 6.1).

HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events schedule. HIV-associated conditions will be assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (Appendix 1). Indicators of clinical disease progression are defined as:

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

6.4. Endpoints

6.4.1. Maternal and Infant

Maternal/Uteroplacental outcomes: To characterize pregnancy outcomes (including but not limited to Caesarean section, premature rupture of membranes, pre-term labor [prior to Week 37 of pregnancy], pre-term delivery, preeclampsia, eclampsia, hemolysis-elevated-liver enzymes-low platelet count [HELLP], pre-gestational diabetes, gestational diabetes, hypertension, multiple gestation, chromosomal abnormalities, intrauterine infection, and drug-induced hepatitis).

Infant: To characterize infant outcomes (i.e., infant gestational age, length, weight [including percentiles, SGA, AGA, LGA, IUGR], and head circumference, and presence or absence of major congenital abnormalities) at birth.

Infant

6.4.2. Efficacy

- Proportion of subjects with plasma HIV-1 RNA < 50 c/mL over time ;
- Proportion of subjects with plasma HIV-1 RNA < 400 c/mL over time
- Absolute values and changes from Baseline in CD4+ T cell counts over time;
- Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).

6.5. Safety

Safety assessments will be conducted to characterize the safety and tolerability of DTG/ABC/3TC FDC administered during pregnancy according to the Time and Events schedule (Section 6.1) and includes:

- Monitoring and recording all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 6.5.12.
- Regular monitoring of hematology and blood chemistry (parameters to be tested listed below).
- Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the CRF. Abnormalities noted during any exam must be recorded in the CRF (e.g., in the current medical conditions or AE logs).
- Monitoring and recording birth and maternal outcomes (see Section 6.4.1)

Note: Because obstetric and/or pediatric care will not be specifically provided via this study, the subject must also establish appropriate obstetric and pediatric care (including prenatal care) per local standard of care (SoC) in parallel. It will be necessary for the subject to provide a release of medical information for both herself and her infant to her

obstetric and pediatric care providers to facilitate collection of delivery, birth and infant outcomes by the investigator.

- Periodic assessment of urinalysis parameters as described below;
- Evaluation and documentation of all concomitant medications and blood products;
- Suicidality monitoring using the Columbia Suicide-Severity Rating Scale (Section 6.5.10).

Any appropriately qualified site personnel (e.g., Investigator, sub-Investigator, or study coordinator/nurse) can perform assessments. A central laboratory chosen by GSK will undertake all routine scheduled laboratory evaluations within the study. Refer to the central laboratory manual for specific instructions on sample collection, processing, storage, and shipping for each laboratory test.

Table 5 Maternal Laboratory Assessments

Hematology	
Platelet Count	Automated WBC Differential:
Red Blood Count	Neutrophils
White Blood Count (WBC) absolute	Lymphocytes
Hemoglobin	Monocytes
Hematocrit	Eosinophils
Mean Corpuscular Volume	Basophils

Clinical Chemistry			
alpha1-acid glycoprotein (AAG)	Sodium	Lipase	Phosphate
Blood Urea Nitrogen	Potassium	AST	Total bilirubin*
Creatinine	Chloride	ALT	Albumin
Glucose	Total CO_2	Alkaline phosphatase	CPK

*Direct bilirubin will be reflexively performed for all total bilirubin values > 1.5X ULN

Glomerular Filtration Rate (GFR) will be estimated by the central laboratory using the Cockcroft-Gault method [Cockroft, 1976] according to the Time and Events schedule (Section 6.1).

Other Tests
Plasma HIV-1 RNA
CD4+ cell counts
Urinalysis and urine microalbumin/creatinine ratio and urine protein/creatinine ratio

Infant Laboratory Assessment

Laboratory assessment(s) of the newborn is not mandated by this protocol, however, if a laboratory assessment on or after the first day of life is performed per local SoC please collect the following assessment information if available:

Hematology	
Platelet Count	Automated WBC Differential:
Red Blood Count	Neutrophils
White Blood Count (WBC) absolute	Lymphocytes
Hemoglobin	Monocytes
Hematocrit	Eosinophils
Mean Corpuscular Volume	Basophils

If available within 36 hours of delivery please collect the following assessment information if available:

Clinical Chemistry			
	Sodium	-Alkaline phosphatase	Phosphate
Blood Urea Nitrogen	Potassium	AST	Total bilirubin*
Creatinine	Chloride	ALT	Albumin
Glucose	Total CO_2		

In addition, the infant outcomes will also be captured and the following parameters will be captured on the neonate at the time of delivery:

- Gestational age
- Neonatal length and weight
- Neonatal head circumference
- Absence or presence of congenital malformations, with description of malformations where present
- APGAR scores
- SGA, AGA, LGA
- IUGR

HIV status of the infant, if known, should be collected and recorded in the CRF.

6.5.1. Safety Endpoints

- To characterize the safety and tolerability of DTG/ABC/3TC FDC administered during pregnancy, the study will capture the following endpoints for the pregnant women:
  - Incidence and severity of AEs and laboratory abnormalities;
  - Absolute values and changes over time in laboratory parameters;
  - Proportion of subjects who discontinue treatment due to AEs.

- To characterize the safety of DTG/ABC/3TC FDC to the developing fetus, the study will capture the following endpoints:

    - Proportion of pregnancies with and without demonstrated congenital malformations

6.5.2. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the DAIDS toxicity scales (see Section 11.2). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 6.5.5.

IP may be interrupted at the discretion of the Investigator and according to the severity of the AE.

No toxicity-related dose reductions of IP will be allowed. Decisions regarding temporary interruption should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on general subject management and IP interruptions based on the severity of the AE; for specific toxicities, please refer to Section 6.5.3 "Specific Toxicities/Adverse Event Management.

NOTE: In the event of the discontinuation of DTG/ABC/3TC FDC for any reason, reinitiation of this drug should be undertaken with caution. The investigator must obtain a complete history of the events surrounding the discontinuation of DTG/ABC/3TC FDC, evaluate for the possibility of a clinically suspected HSR, and initiate subject management as outlined in the DTG IB, regardless of a subject's *HLA-B*5701* status.

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 6.5.3 "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.

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 the 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.

Subjects with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP.

Exceptions are noted below for lipid abnormalities.

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should 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 the medical monitor. 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.

Subjects with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP. Exceptions are noted below for lipid abnormalities. A FU visit should be performed 4 weeks after the last dose of study medication if AEs or laboratory abnormalities are ongoing.

6.5.3. Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to IP are provided below.

Subjects who permanently discontinue IP for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and FU study evaluations as noted above.

6.5.4. Liver chemistry stopping and follow up 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 <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks;

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

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

- Immediately hold IP.
- Report the event to the medical monitor within 24 hours of learning its occurrence (see Table 5 and Table 6, Section 6.5.12);
- Complete the liver event eCRF and SAE eCRF, where applicable, (see Section 6.5.14.1);
- 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 strongly 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, Toxoplasma IgM or PCR;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Complete blood count (to assess platelets);
- Serum acetaminophen test (APAP adduct test). The site must contact GSK when this test is required. Please refer to the SPM.
- Blood sample for 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 CRF. 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 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.

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, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

Note: Also evaluate for HELLP (Hypertension Elevated Liver enzymes Low Platelets) Syndrome and pregnancy-related steatosis in subjects with ongoing pregnancy.

6.5.4.1. Restarting Investigational Product

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

Approval by ViiV Safety and Labelling Committee (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 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 VSLC.
- Subjects approved by VSLC for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

Refer to Appendix 5, Section 11.5 for further details.

Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by 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 IRB approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved by 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 VSLC.

Subjects approved by the VSLC for restarting IP must return to the clinic once a week for liver chemistry tests until stable, liver chemistries have been demonstrated 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.

Refer to Appendix 5, Section 11.5 for further details.

6.5.4.2. 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) or 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.

6.5.4.3. Decline in Renal Function

Subjects who experience an increase in creatinine from Baseline of 45 μMol/L (or 0.5 mg/dL) without associated evidence for proteinuria should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio should be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study Medical Monitor to discuss additional follow-up and medical management.

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

Subjects who have a decline in CrCL of >50% must return for a confirmatory assessment as soon as possible. A urinalysis and urine total protein/creatinine and microalbumin/creatinine ratios should be done at this confirmatory visit. If the estimated CrCL has declined by >50% (confirmed), then IP should be withheld and the investigator should contact the Study Medical Monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g. other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If IP is reinitiated, it should have been withheld for no more than 4 weeks. If IP is not reinitiated the subject must be withdrawn.

6.5.4.4. Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (>0.3mg/mg, >300mg/g or >34mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio and blood pressure performed, as well as notify the subject's obstetric care provider immediately. If confirmed, then consideration should be made for additional evaluation after consultation with the Study medical monitor and the subject's obstetric care provider for further evaluation. Additional evaluation may include a 24 hr urine protein and creatinine measurement and nephrology referral.

Subjects with an abnormal urine albumin/creatinine ratio (>0.3mg/mg, 300 mg/g or >34mg/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, a repeat blood pressure assessment, and notify the subject's obstetric care provider immediately. If confirmed, with or without evidence of hypertension, the subject's obstetric provider should be immediately contacted. Agreement on further management should be discussed amongst the obstetric care provider, the investigator and Medical Monitor where possible.

6.5.4.5. 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.

Subjects should be managed in terms of a clinically suspected ABC hypersensitivity, as described below.

Note: If allergic reaction is solely pruritus, with no rash, and the subject is in her third trimester of pregnancy the investigator should contact the subject's obstetric care practioner for further evaluation.

6.5.4.6. Abacavir Hypersensitivity Reaction (ABC HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related 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 IB. Investigators must familiarize themselves with this information on ABC HSR in the IB 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 IB) 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 DTG/ABC/3TC (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.**

Essential Patient Information

With reference to the IB 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 ABC that may result in a life-threatening reaction or death and that the risk of a HSR is increased in individuals who are HLA-B*5701 positive.
- Subjects must also be informed that HLA-B*5701 negative individuals can also experience ABC HSR. 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 ABC should be reminded that they must never take any abacavir containing medicinal products (e.g. DTG/ABC/3TC, ZIAGEN, EPZICOM, KIVEXA or TRIZIVIR) again, regardless of their HLA-B*5701 status.
- In order to avoid restarting abacavir, subjects who have experienced a HSR should be asked to return any remaining DTG/ABC/3TC tablets to the Investigator or site staff.
- Subjects who have stopped ABC for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting DTG/ABC/3TC.
- Each subject should be reminded to read the Package Leaflet included in the ABC/3TC 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.

Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH)-E2A definitions of seriousness listed in Section 6.5.5.2, then, in addition to reporting the case as an SAE, the ABC HSR CRF should also be completed within one week of the onset of the hypersensitivity reaction.

6.5.4.7. Skin reactions without other symptoms that are typical of ABC HSR

Including serious skin reactions such as Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), 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 while 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 SJS, 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., DTG/ABC/3TC, 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.

Severe, potentially life-threatening, and fatal skin reactions, including cases of SJS and TEN are listed events in the Local Country Prescribing Information for the first marketed integrase inhibitor, RAL [Isentress US Package Insert, revised April 2013; Isentress EU Summary of Product Characteristics, revised Mar 2013], and hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. For additional information on rash associated with dolutegravir, please see the current version of the DTG IB [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]

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 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 for an isolated Grade 2 rash. However, IP (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 (see Section 6.5.4.). 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 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.

The rash and any associated symptoms should be reported as AEs (see Section 6.5.5) and appropriate toxicity ratings should be used to grade the events (see Appendix 2, 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.

6.5.4.8. Contraception Requirements for the Post-Partum and Continuation Phase Only

A subject will be eligible to enter and participate in the Continuation Phase if she agrees to use one of the following approved methods to avoid a 'new' pregnancy:

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of IP. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

All subjects participating in the study should be counselled on safer sexual practices including the use of effective barrier methods (e.g. male condom/spermicide).

6.5.5. 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.

6.5.5.1. 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.

"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

6.5.5.2. Definition of an SAE

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

- Results in death
- 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.

- 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.

  For this study, hospitalization for a term pregnancy (≥37 weeks gestation) or planned Caesarean section will not be recorded as a SAE. Pre-term delivery or emergency Caesarean section will be recorded as a SAE.

- 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.

- Is a congenital anomaly/birth defect

- 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.

- 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 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 is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.5.6. 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., electrocardiographs, 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. It is important to note that grading for laboratory abnormalities (See Section 11.2) is an objective assessment conducted at the central laboratory and does not translate directly into similarly graded AEs.

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.

6.5.7. 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.

6.5.8. 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 non-cardiovascular death.

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

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

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Appendix 1) will be recorded on the HIV Associated Conditions CRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- the Investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 6.5.5.2), or
- the event or outcome is in the Investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

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.

6.5.10. Suicidality Monitoring

Patients with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). Therefore, it is appropriate to monitor subjects for suicidality 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.

Treatment emergent assessment of suicidality will be monitored during this study using the Columbia Suicide-Severity Rating Scale. The definition of 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. The C-SSRS is to be administered using an interactive voice response system at the time-points specified in Section 6.1.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (Non-serious or SAEs) 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.

6.5.11. Pregnancy

Pregnancy complications (e.g., preeclampsia or eclampsia, prolonged hospitalization after delivery, for wound infections etc, seizures) 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 the 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.

6.5.11.1. Pregnancy Testing during the Post-partum and Continuation Phases

Pregnancy testing will also be conducted during the Post-partum and Continuation Phases as per the Time and Events Table (See Section 6.1) and at anytime during the trial when pregnancy is suspected.

Additionally, a pregnancy test should also be performed prior to IP re-administration, when administration is disrupted for more than 7 days (e.g. temporary interruption of IP) during the Continuation Phase.

6.5.11.2. Action to be taken if Pregnancy occurs

Any female who becomes pregnant (intrauterine) while participating in the Post-partum or Continuation Phase must be withdrawn from the study and discontinue IP.

Any pregnancy that occurs during the Post-partum or Continuation Phase must be reported using a clinical trial pregnancy form, and, to ensure subject safety, must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including pre-term 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 occurring during the Post-partum or Continuation Phase, 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.

6.5.11.2.1. Time Period for Collecting Pregnancy Information

Information on the occurrence of 'new' pregnancies in female subjects during the Post-partum or Continuation Phase will be collected following delivery of the original pregnancy that qualified subjects for participation in ING200336 and ending at the final on-study or Follow-up visit. Follow-up information will only be collected for pregnancies occurring to the final on-study or Follow-up visit.

6.5.12. 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.

If there is an ongoing, unresolved AE and/or SAE at the time of the Withdrawal visit in ING117172, it will be:

- followed for event outcome, which will be recorded in the eCRF, as part of ING117172. (i.e., followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up).
- recorded in the medical history eCRF page as part of ING200336
- any exacerbation or worsening of AEs and/or SAEs from ING117172 during subject participation in ING200336, will be recorded as a new entry in the AE or SAE eCRF pages for ING200336 with a start date reflecting the clinical worsening, and will not be recorded for ING117172.

All SAEs (including those 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 or ViiV concomitant medication) and any non serious AEs of special interest (defined in the study procedure manual) occurring from the withdrawal visit in ING117172 through to administration of IP at Day 1 of ING200336, will be recorded in the eCRF for ING117172.

All AEs and SAEs occurring from Day 1 in ING200336 through to the follow up contact will be collected and recored in the eCRF for ING200336, regardless of relationship to study participation or any other causality.

All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.5.14.

6.5.13. 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?"

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

SAEs and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the Table 6 and Table 7 once the investigator determines that the event meets the protocol definition for that event.

Table 6 Events and Reporting Time Periods for SAEs

	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
Liver chemistry abnormalities for Phase I to IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct)	24 hours[1]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[2]

1. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
2. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

Table 7 Other Events Requiring Prompt Reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Suspected ABC HSR	1 Week	ABC HSR CRF	1 Week	Updated ABC HSR CRF[3]
ALT≥5xULN that persists ≥2 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT ≥8xULN	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT ≥3xULN or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]

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

Table 8 Other Events Requiring Prompt Reporting during the Continuation Phase Only

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form

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.

6.5.14.1. 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, IRB/ 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.

6.5.15. Other Safety Outcomes

Laboratory Assessments

All protocol required maternal laboratory assessments, as defined in Table 4, must be performed by the central laboratory, Quest Diagnostics. 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 labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Quest Diagnostics. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics.

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

6.6. 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 (Section 6.1) for potential viral genotypic and phenotypic analyses ("Plasma for Storage Samples").

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.

6.6.1. Virology Endpoints

Incidence of treatment-emergent genotypic and/or phenotypic resistance in subjects who meet confirmed virologic withdrawal criteria.

6.6.2. HIV-1 pol Viral Genotyping and Phenotyping

Subjects meeting 'confirmed virologic withdrawal criterion' 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 of ING117172 (pre IP) and from samples collected at the time of meeting 'suspected virologic withdrawal criterion' (additional subsequent samples may be analyzed); these results will be reported to the Investigator as soon as available to provide guidance for election of an alternative regimen.

6.6.3. HIV-1 Exploratory Analysis

Additional exploratory analyses for HIV-1 polymerase (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 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from all subjects who have HIV-1 RNA >400 c/mL regardless of confirmatory HIV-1 RNA.

6.7. Pharmacogenetic Research

Information regarding PGx research is included in Appendix 3 (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 Appendix 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.

7. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined 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. 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

This is an open-label, PK and intervention study. No formal hypotheses testing will be performed. An estimation approach will be used to evaluate PK parameters difference between third trimester during pregnancy and at 8-12 weeks postpartum. Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The number of women that will be enrolled into this protocol cannot be established *a priori*, as unintended pregnancies cannot be determined in advance therefore, there is no pre-determined limit on enrollment. Based on the number of pregnancies in the Phase III programs it is estimated there could potentially be approximately 12 subjects in ING117172 who would enroll in this study. The goal is to obtain at 8 subjects providing evaluable DTG PK parameters in the third trimester and postpartum.

8.2.2. Analysis Populations

The Safety and Intent-to-Treat, exposed (ITTE) populations will both be comprised of all patients who have received at least one dose of study treatment medication within this protocol. The Safety population will be used for analyses of safety data and the ITTE population will be used for the analysis of study population and antiviral response data. Further populations may be detailed in the RAP. Analysis Data Sets

8.2.3. Treatment Comparisons

This is a single arm, open-label study therefore there is no treatment comparison.

8.2.4. Interim Analysis

No interim analyses are planned, however further data cuts and analyses may be conducted as necessary to support regulatory requests, submissions and/or publications.

8.2.5. Key Elements of Analysis Plan

For safety and efficacy analyses data gathered after subjects withdraw from IP will be listed but will not be included in summary tables. Data collected from extra visits within a window will be listed 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 planned analyses will be detailed in the clinical study report (CSR).

8.2.5.1. Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical PKs Modeling & Simulation department within GlaxoSmithKline. Plasma DTG concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: area under the plasma concentration time curve at steady state during a dosing interval AUC(0-τ), maximum observed plasma concentration (Cmax), time to Cmax (tmax), pre-dose concentration (C0), concentration at 24h post-dose (Cτ), apparent oral clearance (CL/F), apparent volume of distribution after extravascular (e.g., oral) administration (Vss/F), half-life (t½), unbound DTG concentration in plasma at 3 hours post dose (C3h,u), 24 hours post dose (C24h, u). Weight-normalized CL/F and Vss/F will be calculated as well. CL/F values will be presented in both L/hr and L/hr/kg). Vss/F values will be presented in both L and L/kg.

Unbound fraction (fu) will be calculated using the total and unbound plasma concentration of DTG data generated at 3 and 24 hours post dose for both normal and hepatic impairment subjects using the following formula:

fu = Cunbound/Ctotal

where Cunbound and Ctotal are the unbound and total concentration of DTG in plasma, respectively.

PK data will be presented in graphical and/or tabular form and will be summarized by cohort descriptively. All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GSK.

Log-transformed PK parameters except tmax will be analyzed by analysis of variance (ANOVA). This analysis will consider period (during pregnancy or postpartum) as fixed effect, subject as random effect. The analysis will be performed using the mixed linear models procedure within the SAS/STAT module of the SAS system (Version 9.1 or higher). For each log-transformed PK parameter, point estimate and its associated 90% CI will be constructed for the treatment difference and this difference and its 90%CI will be exponentiated to obtain the ratio of geometric least-squares (GLS) means and its 90% CI. For tmax, Hodeges-Lehmann estimate of difference and 90% CI will be provided.

8.2.5.2. Safety Analyses

Exposure to study medication, measured by the number of weeks on study drug, will be summarized. The proportion of subjects reporting AEs will be tabulated. The following summaries of AEs will be provided:

- Incidence and severity of all AEs

- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs

Laboratory data will be summarized by visit. In addition, the number and percentage of subjects with graded laboratory toxicities (based on DAIDS categories) will be summarized.

SAEs will be summarized and categorized by the DAIDS toxicity scale. The SAE analyses will take place upon closure of the protocol; however, data cuts and analyses may be conducted as necessary in order to support regulatory submissions and/or publications.

Descriptive listings will be provided.

8.2.5.3. Efficacy Analyses

The proportion of subjects with HIV-1 RNA below 400 c/ml at time of delivery observed analysis) and the absolute values and change from baseline in HIV-RNA over time over time will be presented using the OC analysis datasets. Further details of secondary efficacy analyses will be included in the RAP.

8.2.5.4. Viral Genotyping/Phenotyping Analyses

The incidence of treatment emergent genotypic and phenotypic resistance will be summarized. Details of the analyses to be performed will be specified in the RAP.

8.2.5.5. Pharmacogenetic Analyses

See Appendix 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 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:

- IRB/ 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 Appendix 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 CRF 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

Unless terminated early, this study will be considered completed after the last subject completes the last study-related clinic visit or assessment.

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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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11. APPENDICES

11.1. Appendix 1: CDC Classification System for HIV-1 Infections (1993)

Reference - 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR, 1992;41 (No. RR-17):1-19.

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	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 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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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.
   Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
   Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
   Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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

LABORATORY				
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*

LABORATORY					
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

LABORATORY					
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

LABORATORY					
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

LABORATORY					
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 dolutegravir 50mg/abacavir 600mg/lamivudine 300mg.

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 dolutegravir 50mg/abacavir 600mg/lamivudine 300mg. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with dolutegravir 50mg/abacavir 600mg/lamivudine 300mg, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Relationship between genetic variants and the pharmacokinetics and/or pharmacodynamics of DTG/ABC/3TC or other medicines used in this study
- Relationship between genetic variants and safety and/or tolerability of DTG/ABC/3TC or other medicines used in this study
- Relationship between genetic variants and efficacy of DTG/ABC/3TC or other medicines used in this study

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.

In addition to any blood samples taken for the clinical study, a whole blood sample (~6 ml) 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 dolutegravir 50mg/abacavir 600mg/lamivudine 300mg 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 dolutegravir 50mg/abacavir 600mg/lamivudine 300mg.

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 dolutegravir 50mg/abacavir 600mg/lamivudine 300mg. 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: Country Specific Requirements

United Kingdom

This requirement has been included based on requests from the Medicines and Healthcare products Regulatory Agency (MHRA) to include information on the specific duration of the Open-Label/Continuation Phase for similar Phase III trials being conducted with dolutegravir.

Study Duration

The Continuation Phase is intended to provide subjects on DTG/ABC/3TC FDC with post study access to DTG/ABC/3TC FDC until the time to achieve local approval. Therefore, the duration of the Continuation Phase will vary from country to country and is dependent on the recruitment time for the ING117172 (ARIA) study and the time taken to achieve local approval for marketing. However, in the UK, the Continuation Phase will not determine the date of last study treatment administration to subjects. The last date of treatment administration for ING117172 (ARIA) in the randomized study phase is predicted to be February 2016. Because it is a possibility that the last subject on ARIA could present for her final visit pregnant, we have taken into account an additional 9 months for the duration of pregnancy and the 8-12 week post-partum final study visit; therefore the last subject/last visit for ING200336 would be conducted by 28 February 2017.

11.5. Appendix 5: 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 1)
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 2).

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:

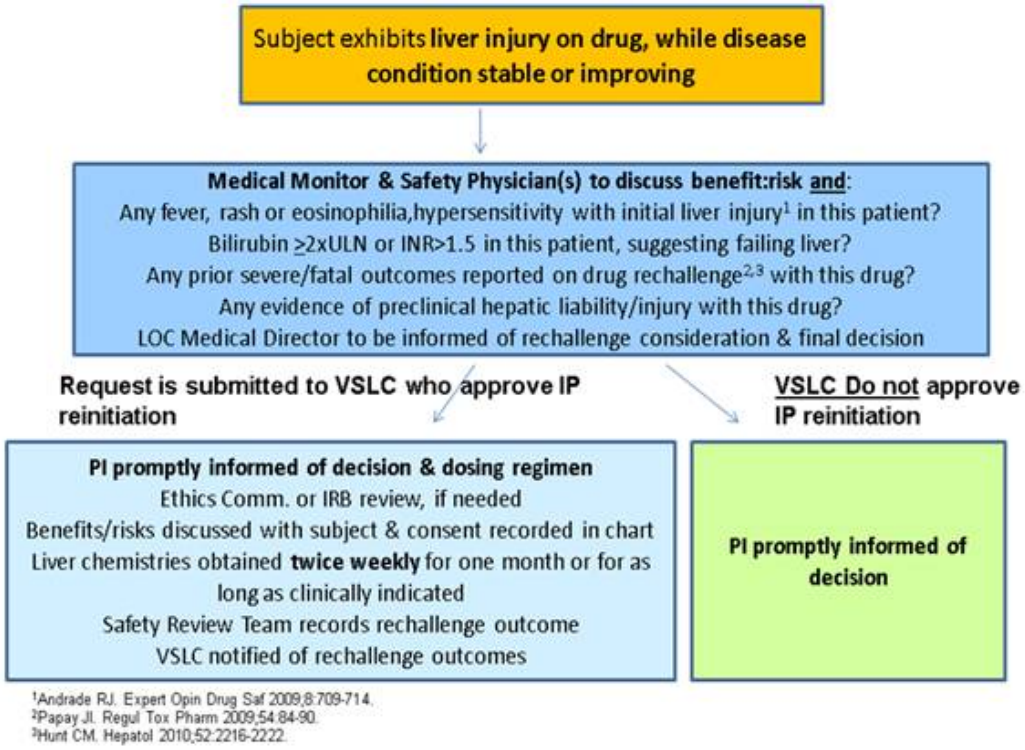
- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin≥2xULN with initial liver injury
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment) [Hunt, 2010]

VSLC Decision Process for Drug Rechallenge Approval or Disapproval (Figure 2):

- 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 2 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 III "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 is drug held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 3):

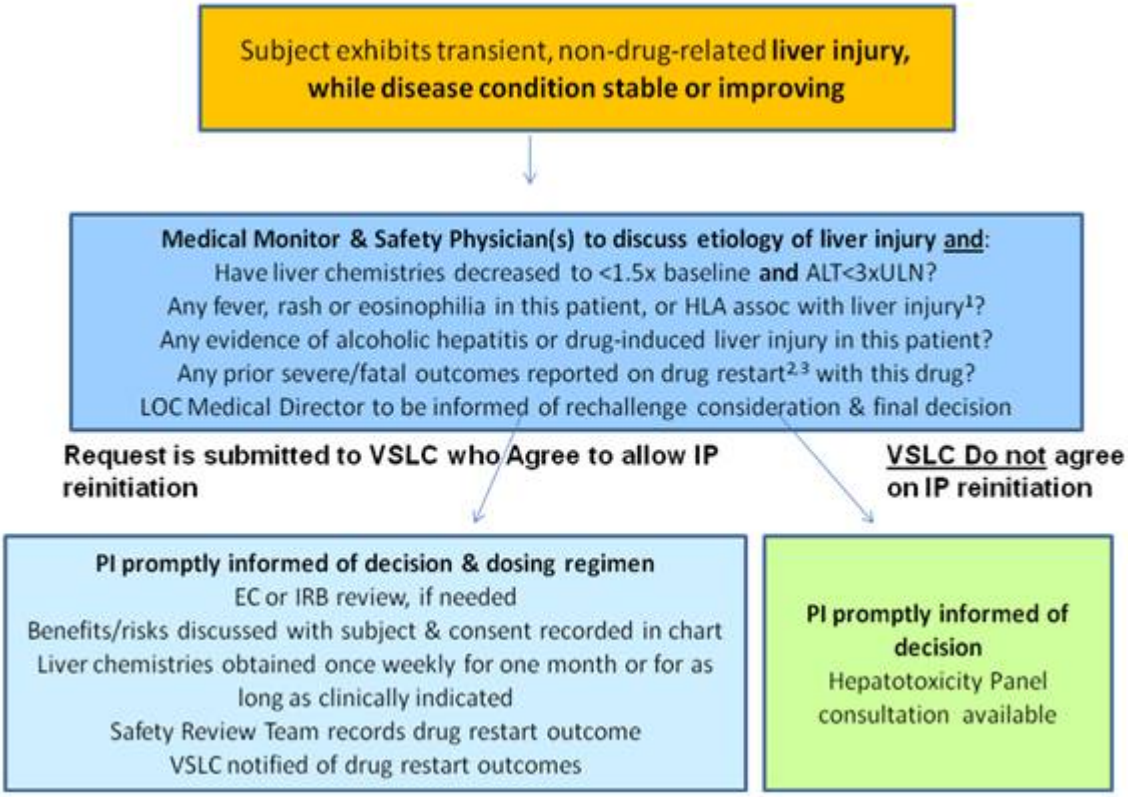
- PI requests consideration of drug re-initiation for a subject stable or improving on IP, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- GSK Medical Monitor and Clinical 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 III 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 3 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 Ethics Committee or Institutional Review Board 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 Ethics Comm. or Institutional Review Board 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

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11.6. Appendix 6: Protocol Amendment Changes

Amendment 01

Removal of Reference in Table of Content

Correction of misspellings in the abbreviation list (LLDO to LLOD, Fumerate to Fumarate, VSS/F [volme to volume)

Section 1: Introduction revised based on newest WHO guidelines

Section 3.1:

- Mothers: addition of "if feasible" to "At delivery**, if feasible,** a cord blood and time-match maternal blood sample will be collected…"
- Addition of "pregnancy outcomes are collected in the eCRF "Delivery Visit"": Please note: In the event of a spontaneous loss of pregnancy during the study, **pregnancy outcomes are collected in the eCRF "Delivery Visit"**.

Section 4.1: removal of "we": Should 12 subjects enroll, this would **likely be sufficient** to obtain at least 8 subjects providing evaluable DTG PK parameters in the third trimester and postpartum.

Section 5.6.2.1: **barbiturates** added to prohibited medication list

Section 6: Study Assessments and Procedures Table

- Added footnote to Medical History and "tick marks" at post-partum and continuation visits.

Note this additional footnote changed the numbering order of the footnotes.

- * footnote, typo correction ("and data" removed)
- [5]Limited PE: heart rate was added
- [7]Intensive PK: note regarding Cord and Maternal blood removed and sentence revised for clarity
- [8]Cord and Maternal Blood footnote added as stand alone footnote
- [13] "methods" added: Note: after delivery, subjects must use one of the contraception **methods** to avoid a 'new' pregnancy

Section 6.2.2.: Important Information on collection of PK samples

- Sentence changed for clarity: If the dosing card is missing, blank, or incomplete, **obtain the missing information** by oral interview by site personnel **and retain in source documents**
- Final paragraph revised: On the days of the PK sampling visits (other than Delivery)

Table 5: Chlorine corrected to **chloride**

Section 6.5.12: Section reference corrected (Section 6.4.1 **to Section 6.5.14**)

References: Cockroft – Typo correction (Pediction to **Prediction**)

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was added as a new appendix, changing Appendix numbers for all other appendices. It's now Appendix 2

Appendix 3 changed to Appendix 4; this UK specific amendment was revised to provide clarity regarding the LSLV

Amendment 02

Amendment 02 corrected typographical errors in Amendment 1:

- Specifically, in the Summary of Revisions, page 1, the reader is referred to Time and Events Table 6; it should be Table 4.

- The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was added as a new appendix, changing numbers of other appendices. It's inclusion also needed to be added to Appendix 6.

- Lastly, where the Summary of Revisions says Appendix 3, it should be Appendix 4.

Protocol Amendment 03

This protocol amendment applies to all participating sites.

Rationale for Protocol Amendment 03:

Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir at the time of conception.

- The Rationale and Risk Assessment sections (Section 1.2. and Section 1.3.1.) were updated to include language regarding risk and mitigation of neural tube defects.
- The Withdrawal Criteria (Section 4.5.) were updated to include a reminder that post-delivery, subjects who desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, should be withdrawn from the study.
- The Time and Events table (Section 6.) was updated to include a footnote to clarify the requirement for pregnancy tests post-delivery, and a reminder for investigators to check at every post-delivery visit that subjects are avoiding pregnancy.
- Contraception Requirements for the Post-Partum and Continuation Phases (Section 6.5.4.8.) were updated with the most recent list of 'highly effective methods for avoiding pregnancy in females of reproductive potential', which excludes the double barrier method of contraception.

Administrative changes were made.

LIST OF SPECIFIC CHANGES

Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

- **Authors**

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- **Title Page**

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- **Section 1.2. Rationale**

~~While no~~**Few** studies have been conducted with DTG in pregnant women, DTG ~~is~~**was** not anticipated to increase the risk of adverse development or reproductive outcomes in humans. **Recently, early results from an unplanned interim analysis of an ongoing birth outcome surveillance study in Botswana showed that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.** Extensive clinical data is available on ABC and 3TC, and this data suggests that the use of ABC and 3TC do not lead to adverse outcomes for the mother or baby when used in pregnancy. Additionally, for women who are already receiving, tolerating and responding virologically to DTG/ABC/3TC, there may be benefit in continuing the regimen after pregnancy is confirmed **(if after the first trimester)**, as the mother may be more likely to continue a familiar and effective regimen. Additional PK, safety and efficacy data is required to further inform the use of DTG and DTG/ABC/3TC in pregnancy.

Section 1.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1,2]
Investigational Product (IP) [DTG/ABC/3TC FDC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
~~Fetuses are most susceptible to potential teratogenic effects of drugs during 1st trimester~~	~~With other ART agents, there are concerns with regard to teratogenicity (e.g., EFV) and maternal hepatic/rash toxicity (i.e., nevirapine).~~ ~~ABC and 3TC have high level of transplacental transfer.~~ ~~Data available for teratogenic risk described in Section 1.2. See the IB and product labels for additional information.~~	~~There is no specific mitigation of risk to the fetus however, the risk is felt to be low based on all available data for DTG, ABC and 3TC. Frequent visits to monitor clinical and laboratory parameters and routine care by the HIV care provider (via this protocol), and routine care by appropriate provider of healthcare to pregnant women~~
Potential teratogenic effects of DTG/ABC/3TC: **DTG: Neural Tube Defects**	The safe use of DTG/ABC/3TC in human pregnancy has not been established. DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals. 3TC and ABC, but not DTG, have been associated with findings in animal reproductive studies but have been used in human pregnancy without evidence for increased risk of teratogenicity. See the **most current** IB for additional information [Antiretroviral Pregnancy Registry Steering Committee, 2013; Vannappagari, 2013; ~~GlaxoSmithKline Document Number RM2007/00683/~~] [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01] . There has been no association between ABC or 3TC and overall birth defects observed in the Antiretroviral Pregnancy Registry (APR), although there are some limitations to these data (http://apregistry.com/index.htm). **In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.**	~~There is no specific mitigation of risk to the fetus however, the risk is felt to be low based on all available data for DTG, ABC and 3TC.~~ **1. A subject is eligible to continue in the study post-delivery if she is not pregnant, and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 6.5.4.8.) until at least 2 weeks after discontinuation of IP.** **2. Subjects who are post-delivery and desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and be withdrawn from the study.** **3. Subjects who are post-delivery are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.** **4. Pregnancy status is monitored at every study visit post-delivery.** Pregnancies must be followed up to determine outcome (including premature termination) and status of mother and child. GSK's central safety department will also forward this information to the APR (Section 6.5.11).

- **Section 4.5. Withdrawal Criteria**

Subjects may be prematurely discontinued from the study for any of the following reasons:

- A new pregnancy during the Continuation Phase as described in Section 3.1. **As a reminder, subjects who are post-delivery and desire to be pregnant, or who state they are not willing/no longer willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.**

- **Section 6. Table 4. Time and Events Table**

Footnote number '15' has been added:

15. Serum pregnancy tests will be performed at the Post-Partum and Continuation Phase visits. Remind subjects who are post-delivery of the need to avoid pregnancy while in the study and adherence to the study's contraception requirements.

Corrections to the footnote referencing have also been made for footnotes 11 and 12.

- **Section 6.5.4.8. Contraception Requirements for the Post-Partum and Continuation Phase Only**

A subject will be eligible to enter and participate in the Continuation Phase if she agrees to use one of the following **approved** methods ~~of contraception~~ to avoid a 'new' pregnancy:

- ~~Complete abstinence from intercourse from delivery, throughout the study, and for at least 2 weeks after discontinuation of all study medications;~~
- ~~Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide);~~
- ~~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 SPM for an example listing of approved IUDs);~~
- ~~Any other method with published data showing that the expected failure rate is <1% per year.~~

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant

2. Intrauterine device or intrauterine system

3. **Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])**
4. **Injectable progestogen [Hatcher, 2011]**
5. **Contraceptive vaginal ring [Hatcher, 2011]**
6. **Percutaneous contraceptive patches [Hatcher, 2011]**
7. **Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.**

Any contraception method must be used consistently, in accordance with the approved product label **and for at least 2 weeks after discontinuation of IP. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.**

All subjects participating in the study should be counselled on safer sexual practices including the use of effective barrier methods (e.g. male condom/spermicide).

- **Section 10. References**

GlaxoSmithKline Document Number 2017N352880_00: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 01, December 2017.

GlaxoSmithKline Document Number 2017N352880_01: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 02, June 2018.

GlaxoSmithKline Document Number RM2007/00683/~~06~~**11**: GSK1349572 Clinical Investigator's Brochure.~~ February 2013.~~ **Version 11, October 2017.**

References to the DTG IB were also updated throughout the protocol to reference the current DTG IB.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.