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ABBREVIATIONS

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
c/mL	Copies per milliliter
CD4	CD4+ Lymphocyte
CDC	Centers for Disease Control and Prevention
C-SSRS	Columbia-Suicidality Severity Rating Scale
CPK	Creatine phosphokinase
CSR	Clinical study report
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
ECG	Electrocardiogram
eCRF	Electronic case report form
EFV	Efavirenz, Sustiva
EVG	Elvitegravir
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV(-1)	Human immunodeficiency virus (type 1)
HSR	Hypersensitivity reaction
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IN(I)	Integrase (inhibitor)
IP	Investigational product
ITT-E	Intent-to-Treat Exposed
ITT-O	Intent-to-Treat Open Label Extension
LDL	Low density lipoprotein
LN	Lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MSDF	Missing, Switch or Discontinuation = Failure
MTB	Mycobacterium tuberculosis
NCEP	National Cholesterol Education Program
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease inhibitor
PK	Pharmacokinetic

Ral	Raltegravir
RAP	Reporting and analysis plan
RBC	Red blood cell
RNA	Ribonucleic acid
RIF	Rifampicin
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
TB	Tuberculosis
TC	Total cholesterol
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
WBC	White blood cells

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to provide details of planned analyses and data displays for end of study reporting results of study ING117175. These analyses may be included in regulatory submissions, study reports, publications and pricing and reimbursement dossiers.

The analyses detailed in this document are based on the protocol of study ING117175 [GlaxoSmithKline Document Number 2014N190475_02] effective on 10-JUL- 2018 and the Week 48 Reporting and Analysis Plan

Study ING117175 is designed to assess the antiviral activity of dolutegravir (DTG) and efavirenz (EFV) ART-containing regimens through 48 weeks. Safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability will also be explored.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective:

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking Rifampicin (RIF)-containing TB treatment.

2.1.2. Secondary Objectives:

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

2.1.3. Tertiary Objectives:

- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;

- To describe rates of TB treatment success (using the WHO definition [WHO, 2010]) for all subjects;
- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;
- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG PK and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

2.2. Study Endpoints

The antiviral efficacy of DTG was previously assessed at both the Week 24 (interim) and Week 48 (primary) time points by analysing the proportion of subjects from the intent-to-treat-exposed (ITT-E) population with plasma HIV-1 RNA <50 c/mL using the modified FDA Snapshot algorithm. This was reported in the Interim Week 24 and Primary Week 48 Clinical Study Reports (GlaxoSmithKline Document Number 2017N323600_00 and GlaxoSmithKline Document Number 2018N363367_00). Modified Snapshot algorithm (i.e. non-penalised background therapy switch) used in the previous interim analyses for defining response by treating subjects with missing efficacy data as non-responders. However, the Modified Snapshot algorithm will not be appropriate for this final analysis because not all subjects in the DTG arm will reach a common time point (i.e. subjects could have different exposures) as they transition off the study (i.e. complete the OLE phase) when DTG becomes commercially available which could vary across countries/sites. Instead, for this final end of study report, an observed case (OC) dataset for efficacy analyses will be used.

2.2.1. Secondary Analysis Endpoints

- Absolute Values and Changes from baseline in CD4+ counts by visit.
- The incidence and severity of AEs and laboratory abnormalities during the OLE.
- The proportion of subjects who discontinued treatment due to AEs during the OLE.
- Absolute values of laboratory parameters at each visit from Baseline to Last Visit and change from Baseline (laboratory assessments are detailed in Table 12, Appendix).

2.2.2. Other Endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses and death) over time for OLE phase;
- The proportion of subjects with a positive suicidal indication alert result at each visit based on eCSSRS for OLE phase only

2.3. Statistical Hypotheses

No formal statistical hypothesis testing will be performed.

3. STUDY DESIGN

A total of 113 subjects were enrolled on to the study. Prior to the closeout, all ongoing subjects initially randomised to DTG who did not prematurely discontinue from the study and who successfully completed 52 weeks of treatment continued into the open-label extension (OLE) phase until DTG became available and commercially available at their site, the subject no longer derived clinical benefit, or the subject met a protocol-defined reason for discontinuation. Subjects randomized to the EFV arm received EFV through their Week 52 visit only, after which subjects completed the study. Note, sites in South Africa were mandated by the local regulatory authority to continue receiving DTG or EFV for at least 2 years post-Week 52.

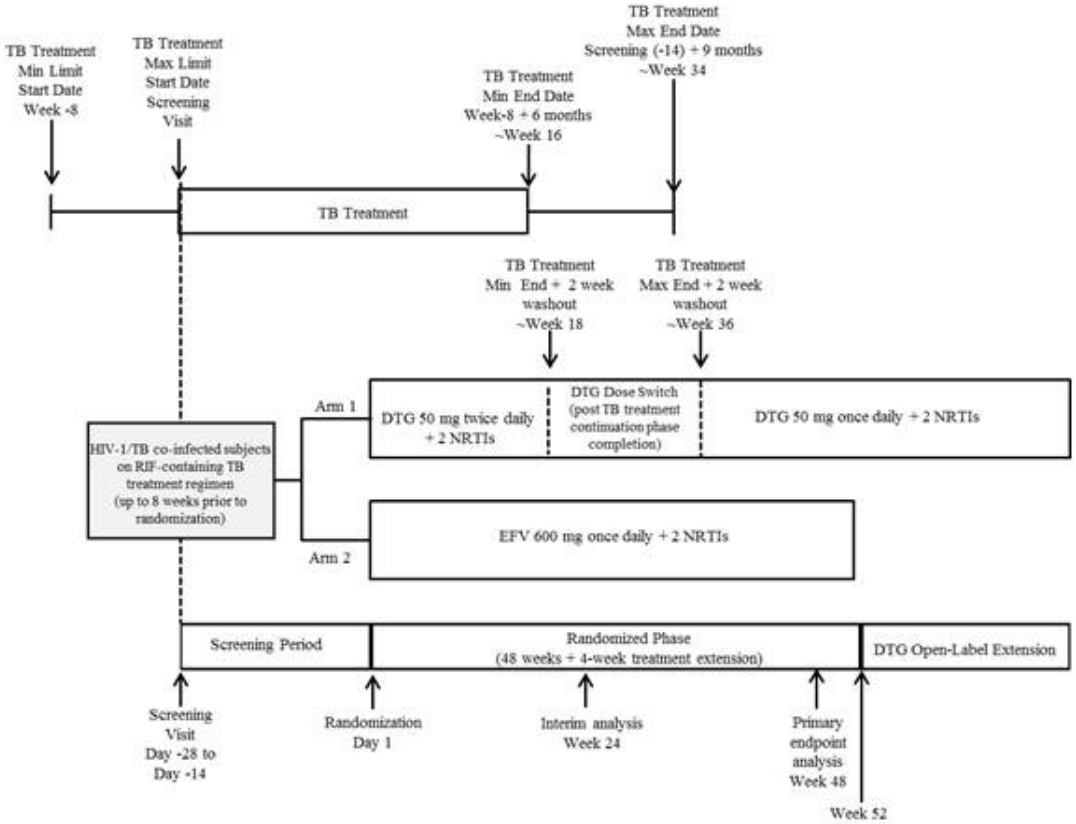
Study ING117175 is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately 125 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or lymph node (LN) *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 75 subjects) or EFV plus 2 NRTIs as active control (approximately 50 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to Week 48 plus a 4-week extension), and a DTG OLE (Figure 1).

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of each HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (see Protocol Table 2) are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

Figure 1 Study Schematic



DTG = dolutegravir; EFV = efavirenz; max = maximum; mg = milligram; min = minimum; NRTI = nucleoside reverse transcriptase inhibitor; NTP = National TB Control Program; RIF = rifampicin; TB = tuberculosis

Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

3.1. DTG Open-Label Extension

Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the DTG OLE. Note, sites in South Africa were mandated by the local regulatory authority to continue receiving DTG or EFV for at least 2 years post-Week 52.

If DTG is locally approved and commercially available when a subject successfully completes the Randomized Phase, the subject will be considered to have completed the study (see Protocol Section 3.1.3) and will need to have alternate arrangements in place to access DTG and NRTIs. If DTG is not locally approved and commercially available when a subject successfully completes the Randomized Phase, he/she will have the opportunity to enter into the DTG OLE. During the DTG OLE, subjects will be supplied with DTG until it is locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Subjects who enter the DTG OLE will be monitored accordingly every 12 weeks.

Subjects who continued into the OLE were required to undergo the clinical and laboratory assessments detailed in Table 12 (Appendix) at Week 60 and every 12 weeks thereafter, at study withdrawal and at follow-up, if required. Results will not be reported for TB outcomes or pharmacokinetics as these data were not collected during the OLE.

3.2. Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Non South African Subjects randomized to EFV plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit;
- Randomized to DTG plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit; and did not enter the DTG OLE;
- Randomized to DTG plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the DTG OLE (defined as remaining on study until commercial supplies of DTG become locally available).
- Subjects from South Africa who are randomized to EFV plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the agreed 2 years extension phase (defined as remaining on study until Week 156)).

3.3. Follow-up

Subjects with ongoing AEs or laboratory abnormalities will attend a Follow-up visit approximately 4 weeks after their last dose of IP (DTG or EFV). Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). The Follow-up visit is not required for successful completion of the study.

4. PLANNED ANALYSES

4.1. Interim Analyses

The first interim analysis was conducted when all subjects completed their Week 24 visit. The primary analysis was conducted when all subjects completed their Week 52 visit. Details of interim analyses was documented in RAP final version 1.4 effective on June-16-2017 and the Interim Week 24 and Primary Week 48 Clinical Study Reports (GlaxoSmithKline Document Number 2017N323600_00 and GlaxoSmithKline Document Number 2018N363367_00).

4.2. Final Analysis

A final end-of-study analysis will be conducted when the final subject randomly assigned to the DTG OLE has transitioned to commercial supplies of DTG or has been withdrawn or when the final subject from South Africa randomly assigned to the EFV has completed the Week 156 extension phase or has been withdrawn from the study, which ever comes last.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

Details of sample size assumption is documented in RAP final version 1.4 effective on June-16-2017

5.2. Sample Size Re-estimation

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

6. ANALYSIS POPULATIONS

6.1. Analysis Populations

The following populations will be assessed.

6.1.1. All Subjects Screened Population

The All Subjects Screened population will consist of all subjects screened for inclusion in the study.

6.1.2. Randomized Population

The Randomized population will consist of all subjects who are randomized in the study and will be used for selected Study Population data listings.

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

The intent-to-treat exposed (ITT-E) population will consist of all randomly assigned subjects who receive at least one dose of IP. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received.

6.1.4. Intent-to-Treat OLE Exposed (ITT-O) Population

The intent-to-treat OLE exposed (ITT-O) population will consist of all subjects in ITT-E population who entered the OLE phase. Patients who have any visit record from Week 60 onwards until the end of the study are classed as entering OLE.

6.1.5. Safety Population

The safety population is defined as all subjects who receive at least one dose of IP. Subjects will be analysed according to the actual treatments received.

If a subject receives treatment differing from that assigned by the randomization schedule (for either a portion of or the entire time on study), they will be included based on the treatment taken for the majority of study participation.

6.1.6. Safety OLE Population

The safety OLE population will consist of all subjects in safety population who entered the OLE phase.

6.1.7. Viral Genotypic Population

The Viral Genotypic population will consist of all subjects in the ITT-E population with available On-treatment genotypic data at the time confirmed virologic withdrawal criterion is met (see ING117175 protocol, Section 4.6.1). This population will be used for analysis of On-treatment and treatment-emergent genotype.

On-treatment genotype testing is done On-treatment, post Day-1 (see Table 7, Section 9.3.1). Treatment-emergent genotypic mutations are defined as mutations that appear between baseline and an On-treatment assessment (e.g., at time of confirmed virologic withdrawal).

6.1.8. Viral Phenotypic Population

The Viral Phenotypic population will consist of all subjects in the ITT-E population with available On-treatment phenotypic resistance data at the time confirmed virologic withdrawal criterion is met (see ING117175 protocol, Section 4.6.1). This population will be used for analysis of On-treatment and treatment-emergent phenotype.

6.2. Analysis Datasets

Final analysis will be performed after the final database lock.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by subject, study period or phase, day, and time, noting treatment arm; summaries will be presented by treatment arm, day, and time.

Version 9.4 or higher of the SAS system will be used to analyse the data and to generate tables, figures, and listings.

6.2.1. Observed Case

The observed case (OC) dataset uses only the data that is available at a particular time point, with no imputation for missing values. This data will be used primarily for safety analyses and for some analyses of efficacy.

7. TREATMENT COMPARISONS

7.1. Primary Comparison of Interest

No formal treatment comparisons will be performed in this study.

7.2. Data Display Treatment Descriptors

In data displays, treatment groups will be defined as shown in Table 1.

Table 1 Data Display Treatment Descriptors

Treatment Group	Descriptor
DTG	DTG plus 2 NRTIs (DTG 50 mg twice-daily with 2 NRTIs until 2 weeks after completing TB therapy, then DTG 50 mg once daily with 2 NRTIs)
EFV	EFV 600 mg once daily plus 2 NRTIs

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Multicenter Studies

Data will be summarized for all centers combined. Country will be treated as an exploratory subgroup for analyses of the primary efficacy endpoint as described in Section 8.3.

8.2. Multiplicity and multiple comparisons

No adjustments for multiplicity are required as no formal statistical hypothesis testing will be performed. No multiple comparisons will be performed.

8.3. Virology

Genotypic and phenotypic testing will be conducted for subjects meeting confirmed virologic withdrawal criteria, i.e., confirmed HIV-1 RNA ≥400 c/mL from Week 24 onwards. The samples from Day 1 and from the "suspected virologic withdrawal criterion" visit will be tested (i.e., the first of the two consecutive results ≥400 c/mL). Treatment-emergent genotypic and phenotypic resistance will be investigated for the Viral Genotypic/Phenotypic populations, respectively.

8.3.1. Genotype

An assessment will be made of every change across all amino acids within the IN encoding region at Day 1 and time of meeting confirmed withdrawal criteria, with particular attention paid to specific amino acid changes associated with the development of resistance to RAL, EVG, or DTG. The known IN mutations associated with the development of resistance to RAL, EVG, or DTG are shown in Table 2.

Table 2 IN Mutations Associated with Development of Resistance to DTG

Known IN mutations associated with the development of resistance to RAL, EVG or DTG:

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, **E92Q/V**/G, Q95K, T97A, G118R, **F121Y**, E138A/K /T, G140A/C/S, **Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R/**N, **V151L**/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, S230R, R263K L68V/I,* L74I/M,* E138D,* V151I,* G193E *

Note: draft listing; may be modified in case of additional substantive data availability.

- INI mutations listed taken from Stanford HIV Resistance Database (http://hivdb.stanford.edu/DR/cgi-bin/rules_scores_hivdb.cgi?class=INI cited 03Feb2017) and accessed on 07Mar 2017.
- Each INI mutation listed had a score of ≥10. INI substitutions listed above in bold had a score of =60.

  * Denotes additional INI mutations added as they were identified during in vitro passage of DTG or seen in a previous DTG study in INI-experienced subjects (ING112574).

Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA) and shown in Table 3 will be evaluated.

Table 3 Major Mutations Associated with Resistance to Other Classes

NRTIs	M41L, A62V, K65R/E/N, D67N, 69 insert, K70R/E, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E
NNRTIs	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I/L
PIs	D30N, V32I, M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M

Note: the most recent information available from IAS-USA (https://www.iasusa.org/content/essential-management-hiv-infection) will be used, should it be revised before the time of analysis. This table is based on January 2017 revisions.

8.3.2. Phenotype

Phenotypic susceptibility to all licensed antiretroviral drugs, including DTG and EFV, will be determined using PhenoSense HIV assays from Monogram Inc. and will be reported as fold change (FC) in IC_{50} relative to wild-type control virus NL4-3, i.e., FC of sample virus = IC_{50} of sample virus/IC_{50} of control virus. Since the maximum assay limit for FC for each ART varies from subject to subject, FC values that are greater than the maximum assay limit (e.g., '>100') will be interpreted as having a value equal to the smallest maximum assay limit for that ART in the study population for data analysis. Censored values will be presented 'as is' in the listings. Phenotypic susceptibilities will be categorised according to FC as shown in Table 4 (based on Monogram PhenoSense assay). Clinical cutoffs (where available) or biological cutoffs by PhenoSense will be used to define the phenotypic susceptibility of background treatment.

Replication capacity is generated as part of standard phenotypic assays.

Table 4 Clinical and Biological Cutoff Values for the PhenoSense HIV Drug Resistance Assay

Drug	Abbreviation	Class	PhenoSense cutoff
Abacavir	ABC	NRTI	(4.5 – 6.5)[a]
Lamivudine	3TC	NRTI	3.5 [a]
Didanosine	ddI	NRTI	(1.3 – 2.2) [a]
Stavudine	d4T	NRTI	1.7 [a]
Zidovudine	AZT (ZDV)	NRTI	1.9[b]
Emtricitabine	FTC	NRTI	3.5[b]
Tenofovir	TDF	NRTI	(1.4 – 4) [a]
Delavirdine	DLV	NNRTI	6.2[b]
Efavirenz	EFV	NNRTI	3[b]
Nevirapine	NVP	NNRTI	4.5[b]
Etravirine	ETR	NNRTI	(2.9 – 10)[a]
Rilpivirine	RPV	NNRTI	2[b]
Fosamprenavir/r	FPV/r	PI	(4 – 11) [a]
Atazanavir/r	ATV/r	PI	5.2 [a]
Indinavir/r	IDV/r	PI	10 [a]
Lopinavir/r	LPV/r	PI	(9 – 55) [a]
Nelfinavir	NFV	PI	3.6[b]
Saquinavir/r	SQV/r	PI	(2.3 – 12) [a]
Tipranavir/r	TPV/r	PI	(2 – 8) [a]
Darunavir/r	DRV/r	PI	(10 – 90) [a]
Raltegravir	RAL	INI	1.5[b]
Elvitegravir	ELV	INI	2.5 [b]
Dolutegravir	DTG	INI	(4 – 13)[a]

a. clinical cutoff (lower cutoff – higher cutoff)
b. biological cutoff

Clinical cutoffs (where available) or biological cutoffs by PhenoSense will be used to define the phenotypic susceptibility to each drug in a subject's background regimen.

Biological/Clinical Cutoff:

Fold Change	Interpretation
> clinical lower cut-off or biologic cut-off	resistance
≤clinical lower cut-off or biologic cut-off	sensitive

Clinical Cutoff:

Fold Change	Interpretation
> clinical higher cut-off	resistance
≤clinical higher cut-off and > clinical lower cut-off	partially sensitive
≤clinical lower cut-off	sensitive

8.4 Combining Treatment Phases and States

On-treatment and Post-treatment assessments and events will be classified as occurring during the Randomized or OLE Phase of the study as follow:

- If a subject did not enter the OLE Phase, then any Post-treatment data will be assigned to the Randomized Phase.
- For subjects who did enter the OLE Phase, any Post-treatment data will be assigned to the OLE Phase.

8.5 Data Reporting

Summary outputs for end of study analysis will include all available data at the time of data base lock from the OLE Phase, unless otherwise stated. A few selected outputs will report all available data from both Randomized and OLE phases. Output titles will denote the phase(s) that they report data from.

9. DATA HANDLING CONVENTIONS

All data manipulations, tabulations, calculations, and figures will be performed using SAS Version 9.4 or higher on a system of WINDOWS computers.

9.1. Premature Withdrawal and Missing Data

9.1.1. Methods for Other Data

For other laboratory data (e.g., HIV-1 RNA as a continuous measure, CD4+ cell counts, haematology, and clinical chemistry) no imputation for missing data or premature discontinuation will be performed and the observed values will be used.

9.1.2. Methods for Missing Dates

9.1.2.1. Date of Birth

Due to local privacy regulations, only the year of birth is recorded in the eCRF. The following algorithm will be used for imputation:

- All dates of birth will be imputed using the 30th day of June.

Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.

In listings of demographic data, the year of birth as entered will be displayed.

9.1.2.2. Adverse Events

The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:

- For a missing start day, the 1st of the month will be used unless this is on the same month but before the start date of investigational product; in this case the IP start date will be used (and hence the event is considered On-treatment as per Section 9.3.1).
- For a missing stop day, the last day of the month (28th, 29th, 30th, or 31st as appropriate for the month and year) will be used, unless this is on the same month but after the stop date of IP; in this case the IP stop date will be used.

Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

In listings of AE data, the partial start and end dates as entered will be displayed.

9.1.2.3. Concomitant Medications

Missing dates for concomitant medications (including TB medication)/ARTs are handled as described in Section 9.3.5.

9.1.2.4. Exposure

If a partial or a missing IP stop date is recorded in the eCRF while study is ongoing, the following convention will be used:

- if an IP stop date is partial where the day is missing (i.e., MMMYYYY), the last day of the month (28/29/30/31 depending on the month and year), the date of last visit, or the recorded date of withdrawal/completion, whichever is earlier, will be used.
- if an IP stop date is partial where the day and month are missing, the last day of the year i.e., 31DECYYYY, the date of last visit, or the recorded date of withdrawal/completion, whichever is earlier, will be used.
- if an IP stop date is completely missing, the date of last visit or the recorded date of withdrawal/completion, whichever is earlier, will be used.

9.2. Derived and Transformed Data

9.2.1. Age

Age, in whole years, will be calculated with respect to the subject's Screening visit. Only subjects' year of birth is recorded in the eCRF, hence the imputed date of birth (see Section 9.1.2.1) will be used to calculate the subject's age.

9.2.2. Baseline and Change from Baseline

Unless stated otherwise, the baseline value for a parameter (including labs, vital signs, virology assessments, etc.) is defined as the last Pre-treatment (see Section 9.3.1) value observed. This is generally expected to be from the Day 1 visit, although such values may be missing or unscheduled assessments may be performed before treatment start. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.

Change from baseline for a parameter is calculated as (observed value - baseline value).

The percentage change from baseline for a parameter is calculated as

$$\%\ \text{change from baseline} = \frac{\text{observed value} - \text{baseline value}}{\text{baseline value}} \times 100$$

9.2.3. Exposure

A subject's exposure, in days, to investigational product will be calculated as

Exposure = IP Stop Date – IP Start Date + 1

where IP Stop Date is the date of final dose of IP received and IP Start Date is the date of initial dose of IP in the study. If IP Stop Date is partial or missing it will be imputed as Section 9.1.2.4.

An alternative calculation of exposure will be performed where the duration of any dosing interruptions, based on eCRF data, will be subtracted from the result above.

9.2.4. Genotype

A mutation is considered present whenever the encoded amino acid residue differs from the amino acid that would have been encoded by the wild-type (e.g., HXB2, NL43) comparator gene; e.g., Q148K. If the encoded amino acid is seen as a mixture of wild-type and mutant amino acid, e.g., Q148Q/K, the mutated amino acid is considered present at the codon of interest. If the encoded amino acid is seen as a mixture of two or more amino acids, which may or may not include wild type, e.g., Q148K/H or Q148K/H/Q, etc., for the purposes of calculating the number of mutated amino acids, only one mutation is considered to be present at the codon of interest.

Table 5 shows how different amino acid changes will be represented.

Table 5 Representation of Amino Acid Changes

Mutations	Amino acid change
T69S	Single mutation from amino acid 'T' (vendor reference) to 'S' (sample) at codon '69'
Q148H/K/R	Mixture of amino acid mutations 'H', 'K' and 'R' (sample) from amino acid 'Q' (vendor reference) at codon '148'
_69_1T	First insertion of amino acid 'T' (sample) at codon '69'
_69_2S	Second insertion of amino acid 'S' (sample) at codon '69'
_69_3S/A	Third insertion of a mixture of amino acids 'S' and 'A' (sample) at codon '69'
L74L/-	Mixture of amino acid 'L' (sample) and a deletion at codon '74'
V75-	Single deletion of amino acid (sample) at codon '75'

9.2.5. Hepatitis Status

Hepatitis C status will be determined using antibody (IgM or IgG) and/or hepatitis C virus (HCV) RNA. If both antibody and virus RNA assessments are available, the latter will take precedence and positive/negative status will be based on whether HCV RNA is detectable (i.e., ≥43 IU/mL [≥1.63 log IU/mL]) or not.

A subject will be considered positive for hepatitis B virus (HBV) if they have a positive surface antigen or detectable HBV DNA. Although Subject with hepatitis B are excluded from the study, subjects meeting liver stopping criterion will be tested for Hepatitis B, and incident new hepatitis B infection will be listed.

Baseline hepatitis status will be based on Pre-treatment laboratory assessments.

9.2.6. Plasma HIV-1 RNA

For summaries and analyses which use HIV-1 RNA level as a continuous measure, the logarithm to base 10 of the value will be used.

HIV-1 RNA results may be provided as censored values, such as <40 or >9,999,999 c/mL. For the purposes of summary statistics, such values will be replaced by the next value beyond the limit of detection, e.g., 39 or 10,000,000 c/mL, respectively, for the given examples. Data listings will show the censored values as provided.

In addition, HIV-1 RNA results including whether "Target Detected" or "Target Not Detected" for values <40 c/mL will also be presented in a listing.

For the HIV – RNA tables, the latest on-treatment viral load within each week visit window should be used rather than the closest target date.

9.2.7. CD4+ Cell Counts

CD4+ values provided as non-numeric, censored results from the central laboratory e.g., '<0.02' in original units of GI/L will be imputed as 0.019 and '≤0.02' in original units of GI/L will be imputed as 0.02 so that they are converted to standard units of cells/mm^3 and

included in the CD4 summary statistics. The listing will report the censored result as '<20' in the standard units, i.e., equivalent to <0.02 GI/L.

9.2.8. Lab Toxicities

Toxicities will be based on the Division of AIDS (DAIDS) grading system, as specified in the protocol. Toxicity grades provided by the central laboratory do not distinguish between abnormally high or low criteria, when both are relevant for a particular parameter. When summarising toxicity grades for such parameters, they will be categorized as in Table 6 according to whether they are above or below the midpoint of normal range.

Table 6 Categorization of Select Lab Parameters Relative to Midpoint of Normal Range

Parameter	Below Midpoint	Above Midpoint
Fasted glucose	Hypoglycaemia	Hyperglycaemia
Sodium	Hyponatremia	Hypernatremia
Potassium	Hypokalemia	Hyperkalemia

9.2.9. Study Day

The Study Day of an event (e.g., lab assessment, vital sign, and start date of AE or HIV associated condition) will be derived as the number of days between the date of the event and the initial start date of IP as follows:

1. if date of event ≥ start date of IP, then

$$\text{Study Day} = \text{Date of Event} - \text{Start Date of IP} + 1$$

2. if date of event < start date of IP, then

$$\text{Study Day} = \text{Date of Event} - \text{Start Date of IP}$$

Note that the initial start date of IP is considered to be on Study Day 1 and the day before this is Study Day -1; i.e., there is no Study Day 0.

9.2.10. Total Cholesterol / HDL Cholesterol Ratio

When both total cholesterol and HDL cholesterol results are available from the same date for a subject, then the ratio will be calculated by dividing the total cholesterol result by the HDL cholesterol result. The ratio can be classified as follows:

Parameter	Value Range
Total Cholesterol / HDL Ratio	< 3.5
	3.5 to < 4.4
	4.4 to < 5
	≥ 5

9.3. Assessment Windows

9.3.1. Study Phase and Treatment State

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of IP as either Pre-treatment, On-treatment or Post-treatment.

For laboratory data, HIV and TB associated conditions, vital signs, and genotypic and phenotypic data, treatment state will be defined as in Table 7.

Table 7 Treatment State for Laboratory Data, HIV Associated Conditions, Vital Signs, and Genotypic and Phenotypic Data

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
Randomized Phase (Day 1 – Week 48 plus 4-Week Extension)	Pre-Treatment	date ≤ IP Start Date
	On-Treatment	IP Start Date < date ≤ Week 52 Date of Visit (DOV)
		or if withdrawn prior to or at Week 52: IP Start Date < date ≤ IP Stop Date + 1
	Post-Treatment (withdrawn prior to Week 52 or not enter the Extension)	date > IP Stop Date + 1
Open Label Extension	On-treatment	Week 52 DOV < date ≤ IP Stop Date +1
	Post-Treatment	date > IP Stop Date + 1

If the IP Stop Date for any study phase is completely missing, then any assessment after that IP Start Date will be considered to be On-treatment for that study phase.

For adverse events, treatment state will be defined as in Table 8 , where a partial AE start date uses imputation as described in Section 9.1.2.2. In the case of a completely missing start date, the event will be considered to have started On-treatment unless an end date for the AE is provided which is before start of investigational product; in such a case the AE is assigned as Pre-treatment.

Table 8 Treatment State for Adverse Events

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
Randomized Phase (Day 1 – Week 48 plus 4-Week Extension)	Pre-Treatment	date < IP Start Date
	On-Treatment	IP Start Date ≤ date ≤ Week 52 Date of Visit (DOV)
		or if withdrawn prior to Week 52: IP Start Date ≤ date ≤ IP Stop Date
	Post-Treatment (withdrawn prior to Week 52	date > IP Stop Date

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
	or not enter the DTG Open-Label Extension)	
Extension	On-treatment	Week 52 DOV < date ≤ IP Stop Date
	Post-Treatment	date > IP Stop Date

If the IP Stop Date for any study phase is completely missing, then any event with a start date on or after IP Start Date will be considered to be On-treatment for that study phase. If the start date of the AE for any study phase is after IP Stop Date for that study phase but has been recorded as potentially related to IP, then it will be classified as On-treatment for that study phase.

For reporting purposes, prior, concomitant, and follow-up medications will be classified according to treatment states defined in Section 9.3.5.

9.3.2. Assessment Window Assignment

Withdrawal date from IP/investigational product, laboratory data, vital signs, and genotypic and phenotypic data will be assigned to assessment windows according to actual dates rather than the nominal visit labels as recorded on the eCRF or in the laboratory database.

A window around a target Study Day will typically include all days from the midpoints between it and the target Study Days of the previous and the proceeding visits. In general, the nominal target study day for week *w* is (7**w*)+1.

Based on the Study Day (see Section 9.2.10), assessments are assigned as shown in Table 9 for all endpoints for end of study analysis.

Table 9 Assessment Windows for all endpoints

Study Day of Assessment	Assessment Window	Target Study Day of Window
≤-4	Screen	-28
-3 to 1	Day 1	1
2 to 42	Week 4	29
43 to 70	Week 8	57
71 to 126	Week 12	85
127 to 210	Week 24	169
211 to 294	Week 36	253
295 to 350	Week 48	337
351 to 392	Week 52	365
393 to 462	Week 60	421
(7*w - 41) to (7*w + 42) (Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the extension phase)	Week w w =72, 84, 96,…	7*w + 1
> (Study Day of last dose + 1)	Follow-up	Study Day of last dose + 28

Note for key efficacy time points at Week 24 and Week 48 that the windows have been defined to cover ± 6 weeks, regardless of the midpoint between adjacent target Study Days. The windows for the adjacent periods are adjusted accordingly.

For parameters which are not scheduled to be assessed at particular visits, the all-inclusive windows defined in Table 10 will still be used; however, data summaries will only report scheduled visits. Assessments at unscheduled visits will be included for 'any time On-treatment' time points and in data listings, as well any algorithms that make use of additional data (e.g., Snapshot).

Table 10 Modified Snapshot Assessment Windows

Study Day of Assessment	Assessment Window	Target Study Day of Window
≤-4	Screen	-28
-3 to 1	Day 1	1
2 to 42	Week 4	29
43 to 70	Week 8	57
71 to 126	Week 12	85
127 to 210	Week 24	169
211 to 294	Week 36	253
295 to 378	Week 48	337

9.3.3. Multiple Assessments

If after window assignment there are multiple valid (see Section 9.3.2) assessments of a parameter within the same window and associated with the scheduled Study Phase, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values:

1. the assessment closest to the window target Study Day;
2. if there are multiple assessments equidistant from the target Study Day, then for continuous variables the mean of these values will be used and for categorical variables the worst value.

This is applicable for all parameters except HIV-1 RNA where the latest on-treatment viral load within each week visit window will be used.

Assessments not chosen for use in summary statistics by this algorithm will still appear in the associated listings. Also, such valid assessments will be used when determining values of potential clinical concern for the 'any time On-treatment' time point, and for any algorithm that has specific rules for which observation to use (e.g., Snapshot).

9.3.4. Invalid Laboratory Assessments

Certain laboratory endpoints are required to be collected in a fasting state, i.e., glucose and lipids (total cholesterol, HDL, LDL). If these endpoints are collected in a non-fasting state, then the results will be excluded from summaries; such results will be included in data listings with the fasting status noted.

9.3.5. Classification of Prior, Concomitant, and Post-Therapy Medications

Prior medications are those taken (i.e., started) before the start date of Investigational product. Concomitant medications are those taken (i.e., started or continued) at any time between the start date and stop date of IP, inclusive. Prior medications that were continued during this period are also considered as concomitant medications. Post-treatment medications are those started after the stop date of IP. Concomitant medications that were continued during this period are also considered as post-treatment medications.

It will be assumed that medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as IP, it will be assumed that the medication was taken after the subject started taking IP.

Table 11 illustrates how a medication is classified as prior, concomitant, or post-treatment.

Table 11 Prior, Concomitant, and Post-treatment Classification of Medications

	Pre-treatment	On-treatment			Post-treatment		Prior	Concomitant	Post
		IP Start Date		IP Stop Date	IP Stop Date+1				
(a)	x————x						Y	N	N
(b)	x————		————x				Y	Y	N
(c)	x————		————			————x	Y	Y	Y
(d)			x————x				N	Y	N
(e)			x————			————x	N	Y	Y
(f)						x————x	N	N	Y
(g)	?————x						Y	N	N
(h)	?————		————x				Y*	Y	N
(i)	?————		————			————x	Y*	Y*	Y
(j)	x————		————			————?	Y	Y**	Y**
(k)			x————			————?	N	Y	Y**
(l)						x————?	N	N	Y
(m)	?————		————			————?	Y***	Y***	Y***
(n)	x————	x					Y	Y	N
(o)	?————	x					Y*	Y	N
(p)		x	————x				N	Y	N
(q)		x	————	x			N	Y	N
(r)				x	—	————x	N	Y	Y
(s)				x	—	————?	N	Y	Y**
(t)					x	————x	N	N	Y
(u)					x	————?	N	N	Y
(v)			x————	—	x		N	Y	Y

x = start/stop date of medication
? = missing start/stop date of medication
* If a medication is stopped On-treatment or Post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase
** If a medication is started Pre-treatment or On-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the Post-treatment phase

If a partial date is recorded in the eCRF, the following convention will be used to assign the medication:

- if the partial date is a start date, a '01' will be used for missing days and 'Jan' will be used for missing months;
- if the partial date is a stop date, a '28/29/30/31' will be used for the missing day (dependent on the month and year) and 'Dec' will be used for missing months; for medications recorded in the eCRF as prior ART, the earlier of this imputed date or the day before IP start will be used.

The recorded partial date will be displayed in listings.

9.3.6. Post-baseline

Post-baseline refers to the combined time periods of On-treatment and Post-treatment (Section 9.3.1).

9.4. Values of Potential Clinical Importance

The DAIDS version 1.0 grading for severity of laboratory toxicities and clinical adverse events is included in the protocol (Appendix 3, Section 11.3). The central laboratory will flag lab parameter toxicities directly in the provided datasets.

10. STUDY POPULATION

All displays referred to in this section will be presented for the ITT-E population using the treatment groups in Table 1, unless otherwise indicated.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

The mean, median and quartiles will be presented to one decimal place beyond the precision with which the data were captured. The SD will be presented to two decimal places beyond the precision with which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

10.1. Disposition of Subjects

The total number of subjects in each analysis population will be summarized and a listing will present which populations each screened subject belongs to.

Treatment assignment (or none, if failed screening) will be listed by country and site number for all screened subjects. For randomized subjects, a listing will be produced showing the randomized and actual strata, treatment assignments, and start date of IP; any deviations between randomized and actual strata values will be flagged, and this listing will also be ordered by country and site number.

A listing of each subject's study visit dates by country and site will be produced. This listing will indicate study phase (Section 9.3.1), the treatment state (Section 9.3.1) and assessment window (Section 9.3.2) the visit was assigned to.

A summary of subject disposition during OLE period, i.e., the number and percentage of subjects who completed (as defined in the protocol) or withdrew from the study as recorded in the eCRF Study Conclusion page, will be produced. This summary will also include the primary and any sub-reasons for withdrawal. A listing of reasons for subjects who withdrew from the study will be provided.

In addition, a summary of subject disposition by visit from baseline to last visit will be presented. The number of subjects On-treatment at each scheduled visit will be given

along with the number and percentage of subjects who withdrew from the study before the next scheduled visit. This display will include the subject numbers and reason(s) for withdrawal.

10.2. Protocol Deviations

10.2.1. Inclusion / Exclusion Criteria

A listing of subjects and the criteria they deviated from will be produced.

10.3. Demographic and Baseline Characteristics

Demographic characteristics (gender, age, age ranges, race) collected at screening will be summarized. Year of birth, screening assessment date and the demographic characteristics will be listed for each subject.

The five high level FDA race categories and designated Asian subcategories will be summarized along with all combinations of high-level categories which exist in the data. The nine race categories collected will be summarized along with categories for mixed race. A by-subject listing of race will also be produced.

No Mexican subjects entered OLE phase and thus no Mexican subject specific outputs will be created for EOS analysis.

10.4. Dispensing Information

A listing of dispensation information for IP (dates and number of tablets dispensed and returned) will be produced.

10.5. Concomitant Medications

For reporting purposes, medications will be classified as concomitant, and/or post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of investigational product (see Section 9.3.5). Medications will be coded using the GSK Drug coding dictionary.

Concomitant medications during OLE period will be summarized by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1 (body system). Drugs will be displayed according to the ATC classifications of both their ingredient and combination term. The data will also be summarized by ingredient combinations alone.

A summary of the number and percentage of subjects receiving concomitant medications will also be displayed using a method that presents multi-ingredient medications according to their combination ATC classification rather than the classifications of the ingredients. This display will also include single-ingredient medications. Multi-ingredient medications will be labelled according to the sum of their ingredients, e.g., “TYLENOL Cold and Flu” would appear as “CHLORPHENAMINE MALEATE + DEXTROMETHORPHAN HYDROBROMIDE + PARACETAMOL +

PSEUDOEPHEDRINE HYDROCHLORIDE" under the ATC headings for "Nervous System" and "Respiratory System" (the combination's ATC classifications).

Listings of all medications taken by subjects, including any which are only prior or post-treatment, will be produced for all subjects. The relationship between ATC level 1, ingredients and verbatim text for all medications in the study will be listed.

10.6. Concomitant ART

ART medications will also be classified as concomitant, and/or post-treatment according to Section 9.3.5, with the following modifications:

- ART starting on IP stop date will be considered as only post-treatment and not concomitant. It is expected that after discontinuation of IP, a subject may immediately begin taking another ART.
- ART stopping on IP start date will only be considered as prior and not concomitant.

Summaries of concomitant ART during OLE period will be grouped by GSK Drug ATC classification level 4 (which will provide ART class). Classes are INI, NRTI, NNRTI, PI and Other. LAMIVUDINE should be grouped into NRTI.

Concomitant ART and post-treatment ART will be listed.

The relationship between ATC level 4, combination terms, and verbatim text will be listed.

11. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT-E or ITT-O population, unless stated otherwise.

Listings will present all available data, including data from Randomized and OLE phase. Listings will be grouped by the treatment groups of Table 1.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

11.1. Analysis of Antiviral Efficacy

The antiviral efficacy of DTG was previously assessed at both the Week 24 (interim) and Week 48 (primary) time points by analysing the proportion of subjects from the intent-to-treat-exposed (ITT-E) population with plasma HIV-1 RNA <50 c/mL using the modified FDA Snapshot algorithm. This was reported in the Interim Week 24 and Primary Week 48 Clinical Study Reports (GlaxoSmithKline Document Number 2017N323600_00 and GlaxoSmithKline Document Number 2018N363367_00). This is not an appropriate endpoint for the end of study analysis because not all subjects would have the opportunity to reach a common time point (subjects discontinue the study to transition to locally

available DTG or EFV on a continuous basis), and subjects who would still be responders by the modified FDA Snapshot algorithm when transitioning off the study could be counted as non-responders because of their transition to local DTG or EFV and completion of the study is before the EOS timepoint. Instead, for this end of study analysis, an observed data approach will be adopted. Therefore, only the proportion (%) of subjects still on study with last on-treatment viral load <50 c/mL at each visit will be provided for end of study efficacy analysis.

11.1.1. Summaries

For viral load, the proportion (%) of subjects still on study with viral load <50 c/mL at each visit will be summarised using observed data and descriptive statistics (note: the denominator will decrease over time as subjects will be moving off study). Two-sided 95% CI for proportions will be presented using the normal approximation method from Week 4 to Week 48 in alignment with the method used during the Week 48 IA. The Clopper-Pearson method will then be used from Week 60 onwards to analyse the OLE phase in order to produce 95% CIs on later visits with small numbers of patients.

11.1.2. Listings

Study outcomes will be listed.

Quantitative plasma HIV-1 RNA data will be listed including the interpretation of whether the virus is detected or not ('Detected' or 'Not Detected') by the assay.

11.1.3. Figures

Not applicable.

11.2. Secondary Efficacy Analyses

11.2.1. Absolute Values and Changes from baseline in CD4+

The absolute values of CD4+ cell count (cells/mm^3) and the changes from baseline in CD4+ cell count (cells/mm^3) will be summarized by visit using ITT-E population. The absolute values (i.e., observed values) and change from baseline CD4+ values (in cells/mm^3 and percentage of lymphocytes) will be listed.

11.3. Other Efficacy Analyses

11.3.1. Incidence of disease progression (HIV-associated conditions)

A summary of the number and percentage of all Post-baseline HIV associated conditions, including those which are a recurrence of a previous condition, will be presented for OLE phase. A summary excluding recurrences will also be provided. All data will be included in a listing.

12. SAFETY ANALYSES

All safety displays will be based on the safety or safety OLE population, unless stated otherwise. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables. Listings will present all available data, including from later phases which may not be summarized until future study reports. Listings will be grouped by the treatment groups of Table 1. Note, AE tables are only for OLE phase.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

12.1. Extent of Exposure

The first and last doses and any changes/interruptions in dosing of investigator product will be listed for all subjects, together with details of the reason for any dose change/interruption.

Distribution and summary statistics for the duration of exposure to IP (defined in Section 9.2.3) will be presented.

12.2. Adverse Events

Adverse events will be coded using the most recent MedDRA coding dictionary to give a preferred term and a system organ class. These preferred terms and system organ classes will be used when summarising the data. The verbatim text will be used in listings together with the preferred term. A listing of the relationship of preferred term to verbatim text will be presented ordered by system organ class.

The following summaries of Post-baseline AEs (i.e., those with Post-baseline onset date as defined in Section 9.2.9, Section 9.3.1 and Section 9.3.6) will be tabulated for OLE phase:

1. All AEs by system organ class (SOC);
2. Common AEs by overall frequency;
3. All AEs by SOC and maximum toxicity;
4. Common Grade 2-4 AEs by overall frequency;
5. All drug-related AEs by SOC and maximum toxicity;
6. Grade 2-4 drug-related AEs by overall frequency;
7. Serious AEs (SAEs) by SOC including drug-related and fatal status;
8. AEs leading to withdrawal/permanent discontinuation of study treatment;
9. Summary of Common Non-Serious Adverse Events by System Organ Class

Common AEs are those with ≥5% incidence for any treatment. For AEs reported more than once by a subject, the most severe intensity will be included in summaries where applicable.

The following listings of AEs (including those occurring Pre-treatment and Post-treatment) will be provided for both randomized and OLE phases:

1. All AEs;
2. Fatal SAEs;
3. Non-fatal SAEs;
4. AEs leading to permanent discontinuation of investigational product/withdrawal from the study;

Additionally, a listing of subject numbers for the individual adverse events will be presented for all Post-baseline AEs.

12.3. Deaths and Serious Adverse Events

Displays for deaths and SAEs that were reported during the study will be presented as detailed in Section 12.2. A listing of reasons for considering an AE as serious will be produced.

12.4. Adverse Events Leading to Discontinuation of Investigator Product Withdrawal from the Study and Other Significant Adverse Events

Adverse events leading to discontinuation of IP /withdrawal from the study will be reported as detailed in the Section 12.2.

12.5. Suicidality Events

The number and percentage of subjects with a positive suicidal indication alert result by visit and treatment group during OLE period will be summarized, excluding any false positive results. A positive suicidal indication alert is where there is level, 4 or 5 ideation, or any suicidal behaviour. Ideation levels 4 and 5 are where there is ideation but importantly there is intent to act on it. A false positive alert is one where the site determines the subject does not have suicidal risk, and/or there was an error recorded onsite. A listing of subjects who experience possible depression and/or suicidality-related adverse events along with the data from the Columbia-Suicide Severity Rating Scale (C-SSRS) will be listed. The C-SSRS suicidal ideation and behaviour data will also be listed, and a listing of false positive alerts with the investigator adjudication will also be provided.

12.6. Pregnancies

A listing of any subjects becoming pregnant during the study will be provided. The outcomes of any pregnancies will be described in the CSR, where available.

12.7. Clinical Laboratory Evaluations

The following laboratory evaluations will be collected at regular intervals throughout the trial and summarized for OLE period:

- **Clinical chemistry:**
  - liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP);
  - electrolytes: sodium, phosphate, total CO_2, chloride, potassium;
  - renal chemistries: blood urea nitrogen (BUN), creatinine, GFR (estimated by CKD-EPI);
  - other: creatine kinase (creatine phosphokinase [CPK]), lipase, albumin.
- **Hematology:**
  - platelet count, red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin, hematocrit, mean corpuscle volume (MCV);
  - WBC differential (count and %): neutrophils, lymphocytes, monocytes, eosinophils, basophils.

All other lab parameter collected in the database will be only be displayed in the listing.

Data not provided in the GSK standard measurement units by the central laboratory will be converted by PPD using GSK's Integrated Data Standards Library (IDSL) standard conversions in the CONV dataset where necessary. Values for quantitative parameters provided as non-numeric, censored results from the central laboratory (e.g., '>100', '<1.9') will not be used when calculating summary statistics, but such values will be flagged (relative to normal ranges) and used where appropriate.

There was an issue with one of the Q2 instruments measuring creatinine concentrations between 1-Oct-2106 and 13-Jan-2017 and thus some creatinine values collected from this instrument at this period are unreliable. The affected creatinine samples collected from the defective instrument are described in a spreadsheet titled "ING117175 5BD.xlsx" (see also accompanied guidance document titled "Explanation of content in result spreadsheets Final.docx"). Values with "PASS" status were considered to be reliable after an evaluation the vendor performed based on a re-test of a refrigerated sample. If a re-test was not possible, "N/A" (Not Available) was recorded and the creatinine value is considered unreliable (see guidance document) and will be excluded from any analysis and won't be reported in the outputs. The spreadsheet will serve as a guide to flag the unreliable values and exclude these values from any analysis.

12.7.1. Listings

Listings of laboratory data for subjects with abnormalities of potential clinical concern (i.e., Grade 1 or worse for chemistry/hematology) will be presented. These listings will contain normal range flags, fasting flags, and toxicity grades.

12.7.2. Summaries

12.7.2.1. Summary Statistics

Summary statistics for chemistry and hematology observed results, baseline and changes from baseline at each scheduled visit will be presented by treatment group. Creatinine using mg/dL will also be summarized in addition to GSK standard units within the same table.

12.7.2.2. Toxicities

A toxicity is considered emergent if it develops or increases in intensity from baseline. The maximum Post-baseline emergent toxicity grade for each subject will be used within summaries.

The number and percentage of subjects with maximum Post-baseline emergent toxicities for each grade (Grade 1, Grade 2, etc.) will be summarized by parameter for Randomized and OLE phase. Separate summaries will be produced for chemistry parameters and hematology parameters. Shift tables will be produced showing baseline toxicity versus maximum Post-baseline toxicity.

A summary and listing of subjects meeting hepatobiliary laboratory abnormality criteria at any post-Baseline emergent visit (Randomized and OLE phase) will also be produced based on FDA Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009). In addition, a listing of all liver chemistry data for subjects meeting hepatobiliary laboratory abnormality criteria at any post-Baseline emergent visit will also be produced.

12.7.3. Figures

Not applicable.

12.8. Other Safety Measures

12.8.1. Suspected Abacavir Hypersensitivity Reaction (HSR)

Data recorded on the ABC HSR eCRF will be listed.

12.8.2. Liver Events

For subjects with liver chemistry results reaching or exceeding protocol-defined IP stopping criteria, the following data will be listed:

- liver event results exceeding the stopping criteria, and the time of the event relative to the start of IP and to the most recent IP;
- information on liver events that is used in the calculation of the RUCAM score;
- liver biopsy results;
- liver imaging results;

- past and current liver disease medical conditions;
- serology results from liver event follow-up (e.g., HCV RNA, hepatitis A IgM, CMV IgM antibody, etc.).

13. VIRAL GENOTYPING/PHENOTYPING

Listings will present all available data, including from later phases which may not be summarized until future study reports. Listings will be grouped by the treatment groups of Table 1.

14. PHARMACOGENETIC DATA ANALYSES

Refer to the protocol for information on pharmacogenetic analyses (Appendix 11.1).

15. PHARMACOKINETIC AND PHARMACOKINETIC/PHARMACODYNAMIC DATA ANALYSES

Not reported for end of study analysis.

16. REFERENCES

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17. ATTACHMENTS

17.1. Table of Contents for Data Display Specifications

17.1.1. Study Population

The ITT-E or ITT-O Population will be used, except where noted. The outputs are for end of study analysis. The updated list will be provided in the appendix to the RAP revision.

17.1.1.1. Tables

Number	Title	Population	Details/ Comments	IDSL/TST ID
6.1	Summary of Study Populations	All Subjects Screened		SA1
6.2	Summary of Subject Accountability: OLE Phase Conclusion Record	ITT-O		ES1
6.3	Summary of Subject Accountability: Withdrawals from Study Treatment/Investigational Product by Visit	ITT-E		HIV_ES1
6.4	Summary of Number of Subjects by Country and Site ID	ITT-E		
6.5	Summary of Demographic Characteristics - OLE Phase	ITT-O	Exclude height and weight	DM1
6.6	Summary of Age Ranges	All Subjects Screened		DM11
6.7	Summary of Race and Racial Combinations	ITT-O		DM5
6.8	Summary of Race and Racial Combinations Details	ITT-O		DM6
6.9	Summary of Concomitant Medication by Combination Term ATC Level 1 - OLE Phase	ITT-O		CM1b
6.10	Summary of Concomitant Antiretroviral Therapy - OLE Phase	ITT-O		
6.11	Summary of Demographic Characteristics – Randomized and OLE Phase	ITT-E		

17.1.1.2. ICH Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
12.1	Listing of Study Conclusion Record Reasons for Withdrawal	ITT-E		ES2
12.2	Listing of Important Protocol Deviations	ITT-E		
12.3	Listing of Demographic Characteristics	ITT-E		DM2
12.4	Listing of Race	ITT-E		DM9

17.1.1.3. Other Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
13.1	Listing of Study Populations	All Subjects Screened		
13.2	Listing of Subject Recruitment by Country and Site Number	All Subjects Screened		
13.3	Listing of Visit Dates	ITT-E		
13.4	Listing of Investigational Product Accountability	ITT-E		
13.5	Listing of Concomitant and Post-treatment Medications	ITT-E		CM2
13.6	Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text	ITT-E		CM6
13.7	Listing of Concomitant and Post-Treatment Antiretroviral Therapy	ITT-E		CA5
13.8	Listing of Relationship Between ATC Level 4, Combination, and Verbatim Text for ART	ITT-E		CA7

17.1.2. Efficacy

The ITT-E or ITT-O Population will be used. The outputs are for end of study analysis. The updated list will be provided in the appendix to the RAP revision.

17.1.2.1. Tables

Number	Title	Population	Details/ Comments	IDSL/TST ID
7.1	Summary of Proportion of Subjects with Plasma HIV-1 RNA < 50 c/mL by Visit - Randomized and OLE Phase - Observed Case	ITT-E	Observed Case	
7.2	Summary of CD4+ Cell Count (cells/mm^3) by Visit – Randomized and OLE Phase	ITT-E		
7.3	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit – Randomized and OLE Phase	ITT-E		
7.4	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences - OLE Phase	ITT-O		
7.5	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences - OLE Phase	ITT-O		HIV1
7.6	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit and Subgroup - Snapshot Analysis	ITT-E		
7.7	Summary of Study Outcomes (<50 c/mL) at Week 48 by Subgroup - Snapshot Analysis	ITT-E		

17.1.2.2. ICH Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
12.21	Listing of Quantitative Plasma HIV-1 RNA Data	ITT-E		

17.1.2.3. Other Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
13.21	Listing of CD4+ Cell Count Data	ITT-E		
13.22	Listing of HIV-1 Associated Conditions	ITT-E		HIV4
13.23	Listing of Subjects with Confirmed Virologic Withdrawal	ITT-E		

17.1.3. Safety

The Safety or Safety OLE Population will be used, except where noted. The outputs are for end of study analysis. The updated list will be provided in the appendix to the RAP revision.

17.1.3.1. Tables

Number	Title	Population	Details/ Comments	IDSL/TST ID
8.1	Summary of Extent of Exposure to Investigational Product – Randomization and OLE Phases	Safety		
8.2	Summary of All Adverse Events by System Organ Class– OLE Phase	Safety OLE		AE1
8.3	Summary of Common Adverse Events by Overall Frequency– OLE Phase	Safety OLE		AE3
8.4	Summary of All Adverse Events by System Organ Class and Maximum Toxicity– OLE Phase	Safety OLE		AE5
8.5	Summary of Common Grade 2-4 Adverse Events by Overall Frequency– OLE Phase	Safety OLE		AE3
8.6	Summary of All Drug-Related Adverse Events by System Organ Class and Maximum Toxicity – OLE Phase	Safety OLE		AE5
8.7	Summary of Drug-Related Grade 2-4 Adverse Events by Overall Frequency – OLE Phase	Safety OLE		AE3
8.8	Summary of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment – OLE Phase	Safety OLE		AE1
8.9	Summary of Common Non-Serious Adverse Events by System Organ Class – OLE Phase	Safety OLE		AE1 (modified)
8.10	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) – OLE Phase	Safety OLE		AE15
8.11	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) – OLE Phase	Safety OLE		AE16

Number	Title	Population	Details/ Comments	IDSL/TST ID
8.12	Summary of Drug-Related Non-Serious Adverse Events by Overall Frequency – OLE Phase	Safety OLE		
8.13	Summary of Drug-Related Serious Adverse Events by Overall Frequency – OLE Phase	Safety OLE		
8.14	Summary of Chemistry Values by Visit – Randomized and OLE phase	Safety		LB1
8.15	Summary of Chemistry Changes from Baseline by Visit – Randomized and OLE phase	Safety		LB1
8.16	Summary of Hematology Values by Visit – Randomized and OLE phase	Safety		LB1
8.17	Summary of Hematology Changes from Baseline by Visit – Randomized and OLE phase	Safety		LB1
8.18	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities – Randomized and OLE phase	Safety		
8.19	Summary of Maximum Post-Baseline Emergent Hematology Toxicities – Randomized and OLE phase	Safety		
8.20	Summary of Changes in Baseline Toxicity to Maximum Post-Baseline Toxicity – Randomized and OLE phase	Safety		
8.21	Summary of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria from Baseline to Last Visit – Randomized and OLE phase	Safety		
8.22	Summary of True Positive Suicidal Indication Alerts Based on eCSSRS by Visit– OLE Phase	Safety OLE		

17.1.3.2. ICH Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
12.31	Listing of Investigational Product Exposure Data	Safety		HIV_IP5
12.32	Listing of All Adverse Events	Safety		AE8CP
12.32	Listing of Fatal Adverse Events	Safety		AE8CP
12.34	Listing of Non-Fatal Serious Adverse Events	Safety		AE8CP
12.35	Listing of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Investigational Product	Safety		AE8
12.36	Listing of Serious Adverse Events	Safety		
12.37	Listing of Subject Numbers for Individual Adverse Events	Safety OLE		AE7
12.38	Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	Safety OLE		AE2
12.39	Listing of Clinical Chemistry Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	Safety		
12.40	Listing of Hematology Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern	Safety		
12.41	Listing of Reasons for Considering as a Serious Adverse Event	Safety		
12.42	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1-Section 2)	Safety		PSRAE1
12.43	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)	Safety		PSRAE3
12.44	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)	Safety		PSRAE4
12.45	Listing of Possible Suicidality-Related Adverse Event Data (Section 5-Section 8)	Safety		PSRAE5
12.46	Listing of Medical Conditions for	ITT-E	IDSL	MH2

Number	Title	Population	Details/ Comments	IDSL/TST ID
	Subjects with Liver Stopping Events			
12.47	Listing of Substance Use for Subjects with Liver Stopping Events	ITT-E	IDSL	SU2
12.48	Listing of Post Baseline Maximum ALT and Maximum Bilirubin for subjects with ALT>=3xULN	Safety		

17.1.3.3. Other Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
13.31	Listing of Subjects Who Became Pregnant During the Study	Safety		PREG1a
13.32	Listing of Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Behavior Data	Safety		CSSRS4
13.33	Listing of False Positive Suicide Alerts	Safety		
13.34	Listing of Abacavir Hypersensitivity Reaction Record - Exposure to Abacavir	Safety		ABC_HSR_EXPO2
13.35	Listing of Abacavir Hypersensitivity Reaction Record - Subject History of Drug Allergies	Safety		ABC_HSR_DRUG2
13.36	Listing of Abacavir Hypersensitivity Reaction Record - Subject and Family Conditions	Safety		ABC_HSR_COND2
13.37	Listing of Abacavir Hypersensitivity Reaction Record - Skin Rash Details	Safety		ABC_HSR_RASH2
13.38	Listing of Abacavir Hypersensitivity Reaction Record - Symptoms	Safety		ABC_HSR_SYMP4
13.39	Listing of Abacavir Hypersensitivity Reaction Record - Vital Signs	Safety		VS4
13.40	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Excluding Other Symptoms)	Safety		ABC_HSR_SYMP6
13.41	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Other Symptoms)	Safety		ABC_HSR_SYMP7
13.42	Listing of Liver Monitoring/Stopping Event Reporting	Safety		LIVER5

Number	Title	Population	Details/ Comments	IDSL/TST ID
13.43	Listing of Liver Event Information for RUCAM Score	Safety		LIVER6
13.44	Listing of Liver Biopsy Details	Safety		LIVER7
13.45	Listing of Liver Imaging Details	Safety		LIVER8
13.46	Listing of Laboratory Data from Liver Event Follow-Up	Safety		LB5
13.47	Listing of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria	Safety	same categories as Table 8.21	
13.48	Listing of All Liver Chemistry Data for Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria	Safety		LB5

17.1.4. Virology

17.1.4.1. Other Listings

Number	Title	Population	Details/ Comments	IDSL/TST ID
13.51	Listing of Genotypic Data – Confirmed Virological Withdrawal Subjects	Viral Genotypic		
13.52	Listing of Treatment-associated Resistance Mutations – Confirmed Virological Withdrawal Subjects	Viral Genotypic		
13.53	Listing of Phenotypic Data for Confirmed Virological Withdrawal Subjects	Viral Genotypic		
13.54	Listing of Replication Capacity	Viral Genotypic		

17.2. Data Display Specifications

Data display specifications are available upon request.

18. APPENDIX

Table 12 Time and Events Schedule for Open-Label Extension and Study Withdrawal

Procedure	Week 60 and every 12 weeks thereafter	Withdrawal	Follow-Up
Clinical and Other Assessments			
Physical examination	x	x	x
Concomitant medication	x	x	x
HIV-associated conditions	x	x	
Columbia Suicidality Severity Rating Scale	x	x	
Adverse events	x	x	x
Severe adverse events	x	x	x
Laboratory Assessments			
Quantitative plasma HIV-1 RNA PCR	x	x	
Lymphocyte subsets	x	x	
Plasma for storage	x	x	
Clinical chemistry	x	x	x
Haematology	x	x	x
Serum pregnancy test	x	x	

Division: World Wide Development

Retention Category: GRS019

Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for study ING117175: A Phase IIIb, randomized, open-label study of the safety and efficacy of dolutegravir or efavirenz each administered with two NRTIs in HIV-1-infected antiretroviral therapy-naïve adults starting treatment for rifampicin-sensitive tuberculosis

Compound Number: GSK1349572

Version Number Final 1.4

Effective Date: 16-JUN-2017

Description: This reporting and analysis plan contains a description of all planned statistical analyses and data summaries for study ING117175.

Subject: HIV-1 infection, integrase inhibitor, dolutegravir, efavirenz, antiretroviral therapy-naïve, *Mycobacterium tuberculosis*, co-infection

Author's Name, Title and Functional Area:

PPD	Lead Biostatistician, Biostatistics, PPD
PPD	Senior Reviewer, Biostatistics, PPD

Approved through email by:

PPD	Director, Clinical Statistics, GSK	16-JUN-2017

Version/Release Date	Summary of Change
Final 1.0 / 2015-9-11	
Final 1.1 / 2016-11-17	• Add "No external presentation or publication of the Week 24 data or results will occur until at least all subjects have completed the Week 48 visit (primary endpoint visit)" to Section 4.1 • Add Section 11.4
Final 1.2 / 2017-01-27	• Section 9.2.4: Framingham Equation updated to follow D'Agostino et al. 2008 example • Summary of Median time from TB therapy start to start of ART (Day 1 IP Dose 1) added to Section 10.6 and Table 6.28. • New Table Summary of Treatment Status and Reasons for Discontinuation of Study Treatment, added to Mock Shells as Table 6.7 and all other Table numbering updated respectively. • New Table, Summary of Age Ranges, added to Mock Shells as Table 6.11 and all other Table numbering updated respectively • New Listing, Listing of Reasons for Study Treatment Discontinuation, added to Mock Shells as Listing 12.4 and all other Listing numbering updated respectively • New Listing, Listing of Subjects Excluded from Any Population, added to Mock Shells as Listing 12.8 and all other Listing numbering updated respectively • New Table, Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences), added to Mock Shells as Table 8.17 and all other Table numbering updated respectively. • New Listing, Listing of Medical Conditions for Subjects with Liver Stopping Events, added to Mock Shells as Listing 12.52. • New Listing, Listing of Substance Abuse for Subjects with Liver Stopping Events, added to

	Mock Shells as Listing 12.53 • Adjudicated IRIS tables (TB-Associated and General) updated to display info by maximum AE Grade and RAP Section 12.5 and Section 12.6 updated accordingly.
Final 1.3 / 2017-04-28	• Shells updated to only include randomized phase, and new safety tables (Table 8.29 to Table 8.36) add to summarise Randomized and OLE phase • Additional outputs added (7.24, 7.25, 8.37) based on Tigger study • Clarification added about False Positiver Suicide Ideation in RAP Section 12.8, extra Suicides summary table and listing fo false positive ideation added. • Clarification added in RAP Section 12.10 to identify Creatinine lab samples that were taken incorrectly at site and remove them from summaries.
Final 1.4 / 2017-06-20	• Added new population ITT-O for open label extension phase summary table. • Split definitions of Genotypic and Phenotypic population descriptions to be more clear that these are 2 separate populations • Add Bayesian Section and related shells, appendix, references • Updated Summary of Table 8.28 and Listing 13.48 to remove reference of Hys law and include more ULN summaries • Removed mock shells 6.7, 12.4, 8.27 • Updated definition of study population to be aligned with protocol • New Listing 12.54: Listing of Post Baseline Maximum ALT and Maximum Bilirubin for subjects with ALT>=3xULN”

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ABBREVIATIONS

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
c/mL	Copies per milliliter
CD4	CD4+ Lymphocyte
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
C-SSRS	Columbia-Suicidality Severity Rating Scale
CPK	Creatine phosphokinase
CSR	Clinical study report
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EAC	Endpoint adjudication committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EFV	Efavirenz, Sustiva
EVG	Elvitegravir
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV(-1)	Human immunodeficiency virus (type 1)
HSR	Hypersensitivity reaction
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IN(I)	Integrase (inhibitor)
IP	Investigational product
ITT-E	Intent-to-Treat Exposed
ITT-O	Intent-to-Treat Open Label Extension
LDL	Low density lipoprotein
LN	Lymph node
LVH	Left ventricular hypertrophy
MedDRA	Medical Dictionary for Regulatory Activities
mITT-E	Modified Intent-to-Treat (Exposed)
MSDF	Missing, Switch or Discontinuation = Failure

MTB	Mycobacterium tuberculosis
NCEP	National Cholesterol Education Program
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease inhibitor
PK	Pharmacokinetic
Ral	Raltegravir
RAP	Reporting and analysis plan
RBC	Red blood cell
RNA	Ribonucleic acid
RIF	Rifampicin
RT	Reverse transcriptase
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
TB	Tuberculosis
TC	Total cholesterol
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
WBC	White blood cells

Trademark Information

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to provide details of planned analyses and data displays for reporting results of study ING117175. These analyses may be included in regulatory submissions, study reports, publications and pricing and reimbursement dossiers.

The analyses detailed in this document are based on the protocol amendment 1 of study ING117175 [GlaxoSmithKline Document Number 2014N190475_01] effective on 21-MAR- 2016.

Study ING117175 is designed to assess the antiviral activity of dolutegravir (DTG) and efavirenz (EFV) ART-containing regimens through 48 weeks. Safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability will also be explored.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective:

To assess the antiviral activity at 48 weeks of a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily, with 2 NRTIs) in ART-naïve patients with HIV-1 infection taking Rifampicin (RIF)-containing TB treatment.

2.1.2. Secondary Objectives:

- To assess the antiviral activity of DTG and EFV both administered with 2 NRTIs at Week 24;
- To assess the antiviral activity of EFV administered with 2 NRTIs at Week 48;
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48;
- To evaluate the safety, TB-associated immune reconstitution inflammatory syndrome (IRIS), and tolerability in subjects treated with a DTG- or EFV-based regimen concurrently with treatment for TB over time;
- To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks.

2.1.3. Tertiary Objectives:

- To evaluate the incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) over time;
- To describe rates of TB treatment success (using the WHO definition [WHO, 2014]) for all subjects;

- To describe the proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment;
- To evaluate concentrations of DTG and EFV using sparse sampling and to characterize DTG PK and variability during and post TB treatment and to explore the association between DTG and EFV concentrations and antiviral activity at Week 24 and Week 48.

2.2. Study Endpoints

2.2.1. Primary efficacy endpoint

The primary endpoint will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm with non-penalised switch (see Section 9.2.7 for modified Snapshot algorithm where a protocol-permitted single NRTI switch is not penalised regardless of plasma HIV-1 RNA; i.e., Snapshot algorithm with single switch included) for the ITT-E population in the DTG arm.

2.2.2. Secondary efficacy endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 in both DTG and EFV arms using the modified Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the modified Snapshot algorithm in the EFV arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

2.2.3. Tertiary efficacy endpoints

- Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses and death) over time;
- Proportion of subjects with TB treatment success (using the WHO definition);
- Proportion of subjects with pulmonary mycobacteria tuberculosis (MTB) who are sputum culture-negative 2 months after starting TB treatment.

2.2.4. Other endpoints

2.2.4.1. Safety endpoints

- Incidence and severity of all AEs, SAEs, and laboratory abnormalities;
- Proportion of subjects who permanently discontinue Investigational Product (IP) or TB treatment due to AEs or death;

- Proportion of subjects who temporarily discontinue IP and/or TB treatment due to AEs;
- Proportion of subjects with TB-associated IRIS as defined by the IRIS adjudication panel (see Charter for endpoint adjudication committee (EAC) of general and paradoxical TB-associated IRIS cases).
- Proportion of subjects with General IRIS as defined by the IRIS adjudication panel (see Charter for endpoint adjudication committee (EAC) of general and paradoxical TB-associated IRIS cases).

Note: the study medical monitor will review the AE terms and HIV conditions in order to identify potential TB-associated IRIS cases. All potential cases of TB-IRIS will be submitted in a blinded manner to an end-point adjudication panel. Adjudication panel output will be summarised. TB-associated IRIS criteria are described in Protocol Section 6.4.6 and toxicity management for TB-associated IRIS cases are described in Protocol Section 6.4.3.3.

2.2.4.2. Viral endpoint

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria over 24 and 48 weeks. Subjects who meet confirmed virological withdrawal as per Figure 2 and Figure 3 in Protocol Section 4.6.

2.2.4.3. Pharmacokinetic endpoints

An evaluation of concentrations of DTG and EFV measured at Weeks 8, 24, 36, and 48. For the EFV arm, mid-dosing interval samples will be collected at Weeks 8, 24, 36, and 48. For the DTG arm, 1 sample will be collected for each of the following time points relative to IP dose: pre-dose, 1 to 3 hours post-dose, and 4 to 12 hours post-dose at Weeks 8 and 36 as well as 1 sample pre-dose at Weeks 24 and 48.

2.2.5. Post Week 48 Final Analysis

Prior to the study closeout, when commercial DTG (TIVICAY™) is available at their sites from Week 48 visit onwards, all ongoing subjects can withdraw from the study at a time point regardless of their plasma HIV-1 RNA at the transition visit. Thus modified Snapshot algorithm, used in the previous interim analyses for defining response by treating subjects with missing efficacy data as non-responders, would not be appropriate for this final analysis since not all subjects would have reached a common time point, and subjects who could still be responders by modified Snapshot when they withdrew from the study. Instead, for this final end of study report, an observed case (OC) dataset for efficacy analyses will be used.

2.3. Statistical Hypotheses

This study is designed to assess the antiviral effect of treatment with a DTG-containing regimen (50 mg twice daily during TB treatment and for 2 weeks following discontinuation of TB treatment, then 50 mg once daily) at Week 48, when administered

in combination with dual NRTI therapy. No formal statistical hypothesis testing will be performed.

3. STUDY DESIGN

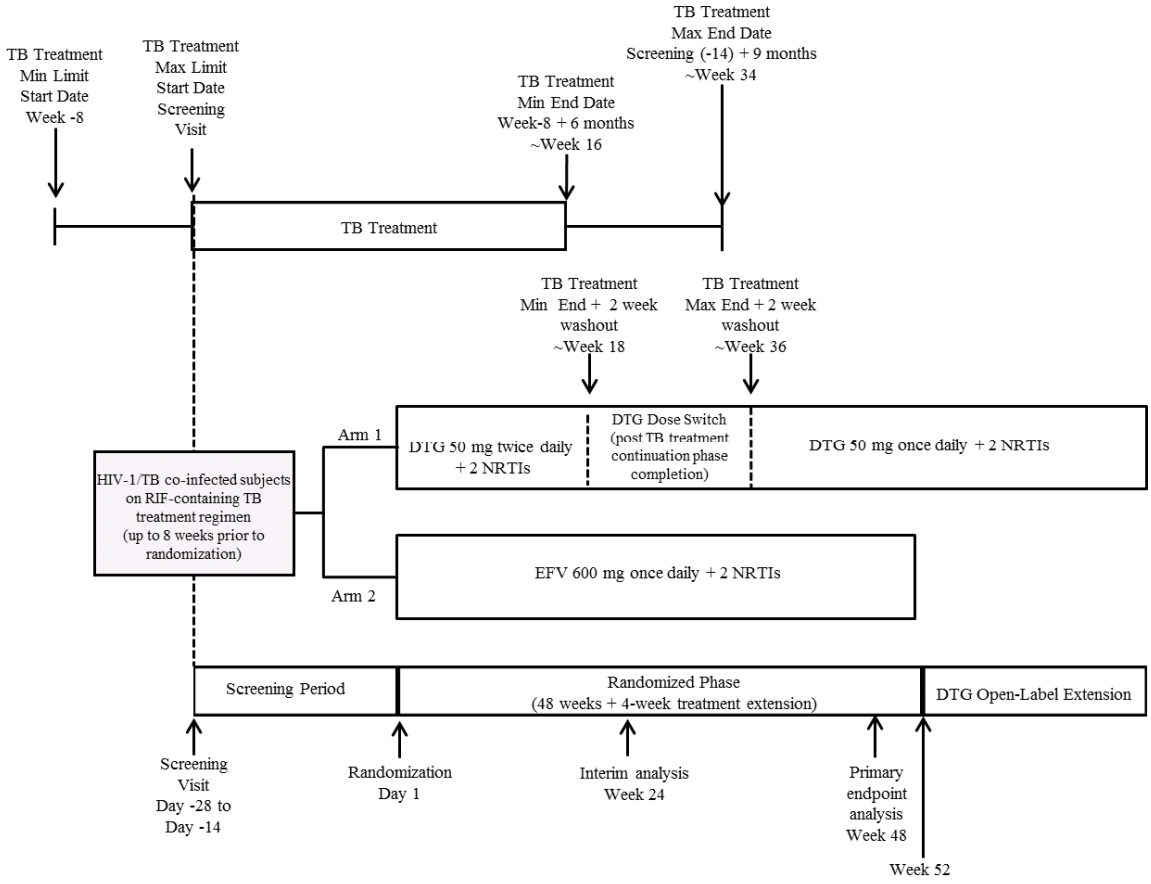
Study ING117175 is a Phase IIIb, randomized, open-label study describing the efficacy and safety of DTG and EFV-containing ART regimens in HIV/TB co-infected patients. The study will be conducted in approximately 125 HIV-1 infected individuals who are ART-naïve with a CD4+ cell count ≥50 cells/mm^3 and newly diagnosed with confirmed pulmonary, pleural, or lymph node (LN) *Mycobacterium* TB (MTB) taking RIF-containing first-line TB treatment. Subjects should have confirmed RIF-sensitive MTB infection as determined by GeneXpert (or equivalent approved molecular test) or mycobacterial culture. Eligible subjects will be randomly assigned in a 3:2 ratio to receive DTG plus 2 NRTIs (approximately 75 subjects) or EFV plus 2 NRTIs as active control (approximately 50 subjects). The dual NRTI backbone will be selected by the investigator in accordance with local standard of care and per current WHO or national guidelines for the treatment of HIV/TB co-infected adults. Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). An interim analysis will be conducted when all subjects complete their Week 24 visit, the primary Week 48 analysis will be conducted when the last subject completes the Randomized Phase, and a final end-of-study analysis will be conducted when the final subject randomly assigned to DTG has transitioned from the Open-Label Extension (OLE) to commercial supplies of DTG or is withdrawn for the study.

This study will include a Screening Period, a Randomized Phase (Day 1 to Week 48 plus a 4-week extension), and a DTG OLE (Figure 1).

Only protocol-defined dose reductions, modifications, or changes in the frequency of any components of each HIV regimen or TB treatment will be allowed at any time in this study, including during the Screening Period.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (see Protocol Table 2) are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be promptly communicated to the study medical monitor.

Figure 1 Study Schematic



DTG = dolutegravir; EFV = efavirenz; max = maximum; mg = milligram; min = minimum; NRTI = nucleoside reverse transcriptase inhibitor; NTP = National TB Control Program; RIF = rifampicin; TB = tuberculosis
Note: TB treatment including isoniazid, RIF, pyrazinamide, and ethambutol will be provided at standard doses by the NTP under program conditions.

3.1. Screening Period

TB diagnosis and confirmation of RIF-sensitive MTB infection must be performed locally. If the result confirming MTB infection is not available before the subject is screened, the assessment can be performed simultaneously in order to screen the subject for the study. Subjects with RIF-resistant TB are not eligible to enter the study. GeneXpert or other molecular test result is required to rule out RIF resistance prior to entry. Mycobacterial culture may be used to confirm RIF-sensitivity (as an alternative to GeneXpert or molecular testing) provided the culture results are available prior to randomization. The 14-day Screening Period may be extended to 28 days to allow receipt of all screening assessment results and to accommodate scheduling. Subjects are allowed to re-screen for this study one time; this will require a new subject ID number. A single repeat test (retest) per analyte or assessment is allowed during the Screening Period to determine eligibility, except for HIV drug resistance testing.

3.2. Randomized Phase (Day 1 to Week 48 plus 4-Week Extension)

As soon as all screening results are available, subjects who fulfill all eligibility requirements will be randomly assigned in 3:2 ratio to receive either DTG or EFV-containing regimens, respectively. DTG or EFV regimens will be started up to 8 weeks after TB treatment initiation and will continue for 48 weeks, plus a 4-week extension.

TB treatment consisting of HRZE for 2 months (i.e., TB treatment intensive phase) followed by HR for 4 or 7 months (i.e., TB treatment continuation phase) will be administered according to local guidelines with TB treatment provided by the National TB Control Programs (NTP) in accordance with national guidelines. Sputum will be collected from subjects with pulmonary tuberculosis 2 months after initiating TB treatment (solid media culture testing is required). Sputum will also be collected at 4 months, 6 months, and 9 months (for subjects who receive TB treatment for 9 months) for smear and culture, for as long as the subject is able to produce sputum. Sputum samples are not required from subjects diagnosed only from pleural or LN aspirates that do not also have pulmonary disease. The same laboratory and method of MTB culture must be used during the study.

Subjects assigned to Arm 1 will receive DTG 50 mg twice-daily with 2 NRTIs until 2 weeks after TB therapy is completed then they will receive DTG 50 mg once daily (with the same NRTI backbone) through the end of the Randomized Phase. Subjects randomized to Arm 2 will receive EFV 600 mg once daily plus 2 NRTIs through the end of the Randomized Phase. The NRTI background regimen selected by the investigator must be determined and documented prior to randomization and should be composed of 2 NRTIs in accordance with the local standard of care and per the WHO or national treatment guidelines for HIV/TB co-infection. Following Day 1, no changes or intensification of background regimen will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of one allowed background NRTI change for management of drug toxicity as described in Protocol Section 6.4.3.

Subjects randomization will be stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3). DTG and EFV will be administered in an open-label fashion throughout the Randomized Phase.

During the Randomized Phase, subjects will attend the clinic at Baseline/Day 1 and at Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

Following the Week 48 visit, subjects will remain on their DTG or EFV-containing regimen for an additional 4 weeks. All subjects will attend the Week 52 visit, although only those with a viral load of ≥50 c/mL at Week 48 will have their viral load confirmed by an assessment at the Week 52 visit. This treatment extension will allow for a more accurate assessment of treatment response for the Week 48 analysis window, as transient increases of HIV-1 RNA levels ≥50 c/mL will not be classified as virologic failure.

To determine DTG and EFV concentrations, sparse plasma samples will be collected at Weeks 8, 24, 36, and 48 in as many subjects as possible. If a subject meets virologic withdrawal criteria, HIV-1 resistance testing will be performed to assess treatment emergent mutations for INIs, NNRTIs, and NRTIs.

3.3. DTG Open-Label Extension

Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the DTG OLE.

If DTG is locally approved and commercially available when a subject successfully completes the Randomized Phase, the subject will be considered to have completed the study (see Protocol Section 3.1.3) and will need to have alternate arrangements in place to access DTG and NRTIs. If DTG is not locally approved and commercially available when a subject successfully completes the Randomized Phase, he/she will have the opportunity to enter into the DTG OLE. During the DTG OLE, subjects will be supplied with DTG until it is locally approved and commercially available, the subject no longer derives clinical benefit, or the subject meets a protocol-defined reason for discontinuation. Subjects who enter the DTG OLE will be monitored accordingly every 12 weeks.

3.4. Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Randomized to EFV plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit;
- Randomized to DTG plus 2 NRTIs and completed the Randomized Phase including the Week 52 visit; and did not enter the DTG OLE;
- Randomized to DTG plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the DTG OLE (defined as remaining on study until commercial supplies of DTG become locally available).
- Subjects from South Africa who are randomized to EFV plus 2 NRTIs, completed the Randomized Phase, including the Week 52 study visit, and entered and completed the agreed 2 years extension phase (defined as remaining on study until Week 156)).

3.5. Follow-up

Subjects with ongoing AEs or laboratory abnormalities will attend a Follow-up visit approximately 4 weeks after their last dose of IP (DTG or EFV). Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). The Follow-up visit is not required for successful completion of the study.

3.6. Independent Data Monitoring

As ING117175 is an open-label study, an Independent Data Monitoring Committee (IDMC) was not set up for this study. Instead, blinded safety data (adverse events, serious adverse events, withdrawals, Grade 3-4 laboratory abnormalities, laboratory tests, vital signs and demographics) from ING117175 will be reviewed on a monthly basis by GSK's internal Safety Review Team using the Clinical Trial Signal Detection tool (Spotfire).

4. PLANNED ANALYSES

4.1. Interim Analyses

The first interim analysis will be conducted when all subjects complete their Week 24 visit. The primary analysis will be conducted when all subjects complete their Week 52 visit. Further data cuts and analyses may be conducted as necessary in order to support regulatory submissions and publications.

No external presentation or publication of the Week 24 data or results will occur until at least all subjects have completed the Week 48 visit (primary endpoint visit).

4.2. Final Analysis

A final end-of-study analysis will be conducted when the final subject randomly assigned to the DTG OLE has transitioned to commercial supplies of DTG or has been withdrawn or when the final subject from South Africa randomly assigned to the EFV has completed the Week 156 extension phase or has been withdrawn from the study, which ever comes last.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

Data from recent DTG studies in treatment-naïve subjects have shown consistent response rates of 88% to 90% at Week 48 with a dose of 50 mg once daily (Table 1). Primary analyses in these studies have shown non-inferiority to RAL 400 mg once daily and superiority to both EFV/TDF/FTC once daily and DRV/r once daily. The proportion of subjects with baseline HIV-1 RNA >100,000 c/mL in the Phase III studies ranged from 25% to 32%; there were few subjects with baseline CD4+ cell counts <50 cells/mm^3.

Table 1 Week 48 Results From Recent Treatment-Naïve DTG Studies

Study	Back-ground NRTI	Endpoint	Active Treatment Response[a]	Comparator/ Control Response	Notes
SINGLE Phase III n=833		Plasma HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg +ABC/3TC once daily 88% (87%)[a]	EFV/TDF/FTC once daily 81% (80%)[a]	DTG superior (at Wk 48/96) Baseline: 32% >100,000 c/mL HIV-1 RNA
SPRING-2 Phase III n=822	ABC/3TC or TDF/FTC	Plasma HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 88% (87%)[a]	RAL 400 mg BID 85% (86%)[a]	DTG non-inferior (at Wk 48/96) Baseline: 28% >100,000 c/mL HIV-1 RNA
FLAMINGO Phase IIIb n=484	ABC/3TC or TDF/FTC	Plasma HIV-1 RNA <50 c/mL; FDA Snapshot	DTG 50 mg once daily 90% (88%)[a]	DRV/r 800 mg/100 mg once daily 83% (80%)[a]	DTG superior at Wk 48 (study continuing to Wk 96) Baseline: 25% >100,000 c/mL HIV-1 RNA
SPRING-1 Phase IIb n=205	ABC/3TC or TDF/FTC	Plasma HIV-1 RNA <50 c/mL; TLOVR	DTG 50 mg once daily 90%	EFV 600 mg once daily 82%	DTG 10 mg 91% DTG 25 mg 88% Baseline: 21% >100,000 c/mL HIV-1 RNA

ABC/3TC = abacavir/lamivudine; c = copies; DRV/r = darunavir + ritonavir; DTG = dolutegravir; EFV = efavirenz; EFV/TDF/FTC = efavirenz/tenofovir disoproxil fumarate/emtricitabine; FDA = Food and Drug Administration (United States); HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; TLOVR = time to loss of virologic response; Wk = week.

a. Response rate for subjects with baseline CD4+ cell count ≥50 to <500 cells/mm^3, where available.

Response rates <50 c/mL in the REFLATE study at Week 48 were much lower than seen in the DTG studies (Table 2). The study population included higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL (46%) and with baseline CD4+ cell counts <50 cells/mm^3 (20%); in particular, the EFV treatment arm had more such subjects than either of the RAL treatment arms. These characteristics are typically associated with a lower response rate for achieving virologic suppression.

Table 2 Week 48 Results from the REFLATE Study

Back-ground NRTI	Endpoint	EFV Once Daily (Response Rate)	RAL Twice-Daily (Response Rate)	Notes
TDF/FTC	Plasma HIV-1 RNA <50 c/mL; Missing=Failure	600 mg (67%)	400 mg (76%) 800 mg (63%)	n=51 in each arm Baseline: CD4+ cells <50 c/mL: 27%, 24%, and 10%[a] HIV-1 RNA >100,000 c/mL: 51%, 39%, 47%[a]

c = copies; EFV = efavirenz; HIV = human immunodeficiency virus; mL = milliliter; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RNA = ribonucleic acid; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

a. Percentage of subjects at Baseline in EFV 600 mg, RAL 400 mg, and RAL 800 mg treatment groups, respectively

Rates of withdrawal due to non-fatal AEs were comparable between REFLATE and the DTG studies. There was a higher incidence of deaths in REFLATE (approximately 5% overall versus <1% in DTG studies) with many owing to complications with TB co-infection. Even accounting for differences in the study population, the REFLATE response rates are lower than would be expected based on results seen in the DTG studies. The smaller sample sizes in REFLATE are more sensitive to what may be other chance findings.

Given the exposure data, it is anticipated that DTG twice daily co-administered with RIF will have efficacy comparable to DTG once daily, but a study population with higher proportions of subjects with baseline HIV-1 RNA >100,000 c/mL and lower CD4+ cell counts would have slightly lower responses than seen in the prior DTG studies.

Assuming an 85% response rate for DTG at Week 48, a sample size of 75 subjects in the DTG arm would have >90% power to detect a response rate of greater than 70%. Although the objective of the study is not to test a statistical hypothesis, the sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of DTG.

5.2. Sample Size Sensitivity

Figure 2 Relationship Between Study Power and Sample Size

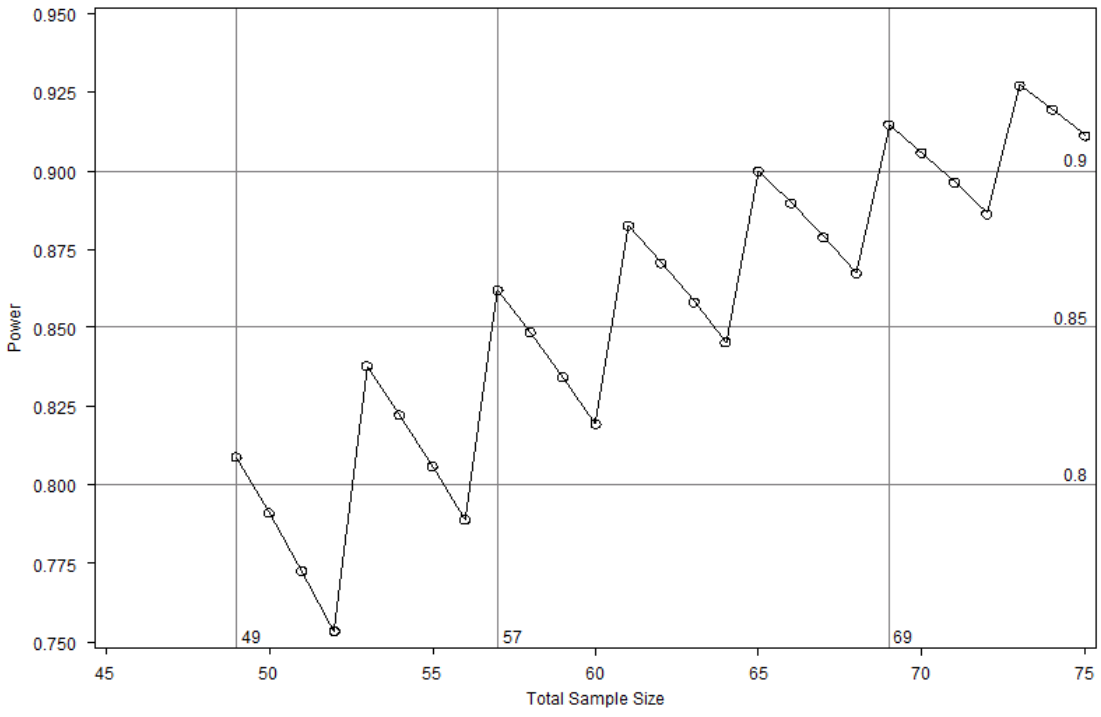


Figure 2 shows the relationship between study power and sample size, assuming an 85% response rate for DTG, to detect a response rate of greater than 70%. A sample size of

75 subjects has >90% power. Smaller samples (e.g., 69 or greater) have at least 88% power, which is relevant when assessing the primary endpoint in alternate analysis populations (i.e., modified ITT-E).

Figure 3 Relationship Between Minimum Sample Size Required and the Assumed Response Rate

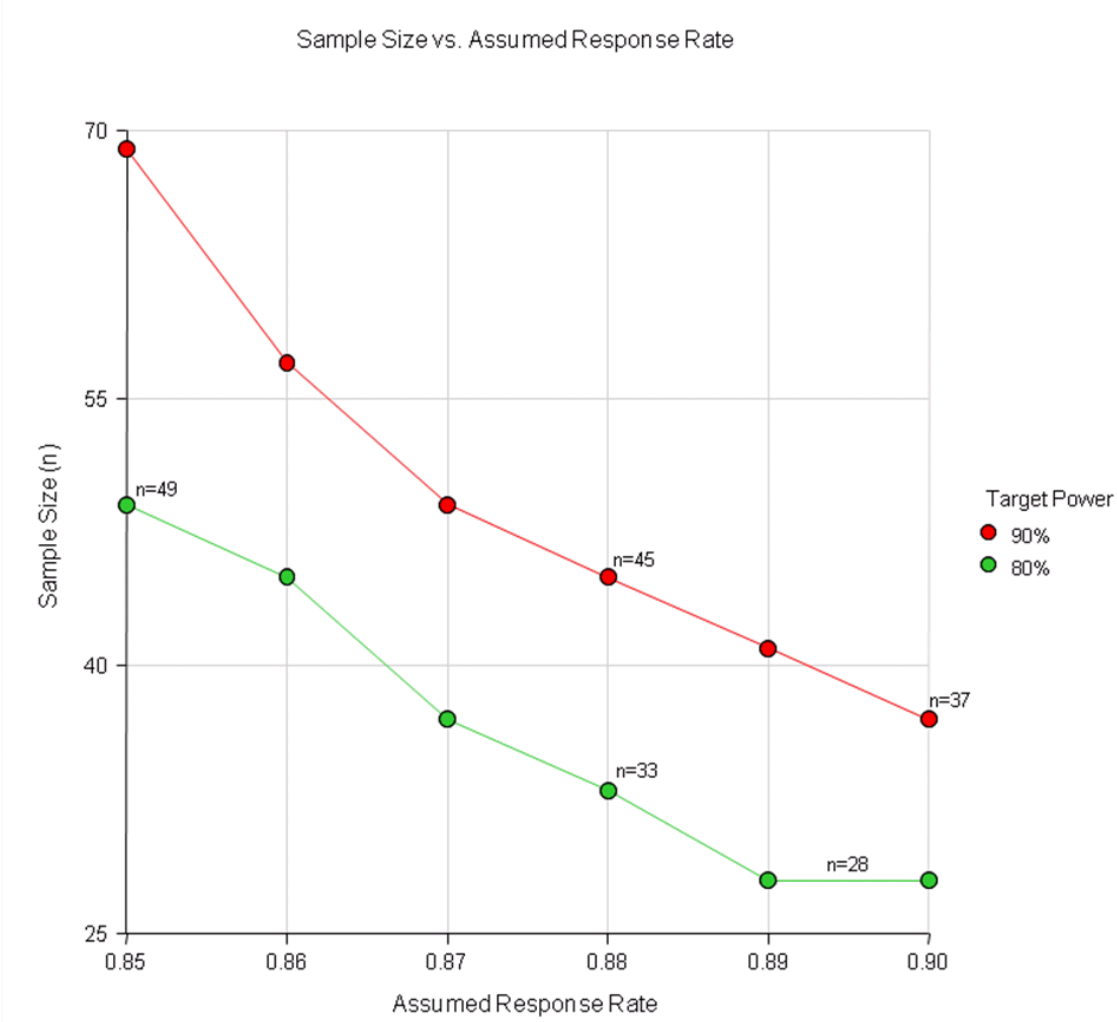


Figure 3 shows the relationship between minimum sample size required and the assumed response rate; different targets for power are considered.

5.3. Sample Size Re-estimation

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

6. ANALYSIS POPULATIONS

6.1. Analysis Populations

The following populations will be assessed.

6.1.1. All Subjects Screened Population

The All Subjects Screened population will consist of all subjects screened for inclusion in the study.

6.1.2. Randomized Population

The Randomized population will consist of all subjects who are randomized in the study and will be used for select Study Population data listings.

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

The intent-to-treat exposed (ITT-E) population will consist of all randomly assigned subjects who receive at least one dose of IP. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received. Unless stated otherwise, the ITT-E population will be used for summaries of efficacy and study population.

6.1.4. Modified Intent-to-Treat Exposed (MITT-E) Population

The modified intent-to-treat exposed (MITT-E) population will consist of all subjects in ITT-E population with confirmed RIF-sensitive MTB. This population will be used in an additional evaluation of the Week 24 snapshot and of the Week 48 primary endpoint.

6.1.5. Intent-to-Treat OLE Exposed (ITT-O) Population

The intent-to-treat OLE exposed (ITT-O) population will consist of all subjects in ITT-E population who entered the OLE phase.

6.1.6. Per-Protocol (PP) Population

The per-protocol (PP) population will consist of subjects in the ITT-E population with the exception of subjects with major protocol violation consisting of not meeting any of the protocol inclusion or exclusion criteria or violations which could affect the assessment of antiviral activity (see Section 10.2). The PP population will be used for sensitivity analyses of the primary efficacy endpoint.

6.1.7. Safety Population

The safety population is defined as all subjects who receive at least one dose of IP. Subjects will be analysed according to the actual treatments received.

If a subject receives treatment differing from that assigned by the randomization schedule (for either a portion of or the entire time on study), they will be included based on the treatment taken for the majority of study participation.

6.1.8. Viral Genotypic Population

The Viral Genotypic population will consist of all subjects in the ITT-E population with available On-treatment genotypic data at the time confirmed virologic withdrawal

criterion is met (see ING117175 protocol, Section 4.6.1). This population will be used for analysis of On-treatment and treatment-emergent genotype.

On-treatment genotype testing is done On-treatment, post Day-1 (see Table 10, Section 9.3.1). Treatment-emergent genotypic mutations are defined as mutations that appear between baseline and an On-treatment assessment (e.g., at time of confirmed virologic withdrawal).

6.1.9. Viral Phenotypic Population

The Viral Phenotypic population will consist of all subjects in the ITT-E population with available On-treatment phenotypic resistance data at the time confirmed virologic withdrawal criterion is met (see ING117175 protocol, Section 4.6.1). This population will be used for analysis of On-treatment and treatment-emergent phenotype.

6.1.10. Pharmacokinetic (PK) Populations

All subjects enrolled in the study who received at least 1 dose of DTG or EFV and for whom any sample was taken for PK analysis with evaluable drug concentration data reported, i.e., no missing date/time of last dose prior to PK sampling, no missing date/time of PK samples, PK sampling performed within acceptable windows (see Section 15) and any drug concentration values deemed anomalous (GSK will evaluate whether the concentration deems anomalous or not) based on known or expected PK characteristics/behaviours of DTG or EFV as agreed between GSK and PPD PK bio-analytical teams.

6.2. Analysis Datasets

Each interim and final analysis will be performed after the database lock of each interim and final database lock.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by subject, study period or phase, day, and time, noting treatment arm; summaries will be presented by treatment arm, day, and time.

Version 9.1 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings.

6.2.1. Modified Snapshot

For all efficacy analysis, each subject's response (i.e., HIV-1 RNA <50 c/mL) will be calculated according to a modified version (i.e. non-penalised background therapy switch) of the US Food and Drug Administration (FDA)'s Snapshot algorithm. According to FDA's Snapshot algorithm substitutions in background therapy (in-class or cross-class) permitted per protocol for documented toxicity reasons are allowed only on or before the first trial visit without penalty. For this study any single protocol allowed background therapy substitution will not be penalised even if occurs after the first trial visit.

The modified Snapshot algorithm will treat all subjects without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to visit window) as non-responders, as well as subjects with ART substitutions not permitted per protocol (see Section 5.1.5). For subjects with HIV-1 RNA data at the visit of interest, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit window of interest (see Section 9.3 Assessment Windows). These are in accordance with FDA's Snapshot algorithm.

Full details on this modified Snapshot algorithm are contained in Section 9.2.7.

6.2.2. Treatment-Related Discontinuation = Failure

The time to meeting confirmed virologic withdrawal criteria or discontinuation due to treatment related reasons (i.e., discontinuation due to drug-related AE, or due to protocol defined safety stopping criteria, [see ING117175 protocol, Section 6.4.3.1], or due to lack of efficacy) will be calculated. Subjects who met confirmed virologic withdrawal criteria or discontinuation due to treatment related reasons is considered as Failure. Subjects who have not met confirmed virologic withdrawal criteria (see ING117175 protocol, Section 4.6) and are ongoing in the study, or who have discontinued for reasons other than those related to treatment, will be censored. This will be the Treatment-Related Discontinuation = Failure (TRDF) data.

6.2.3. Observed Case

The observed case (OC) dataset uses only the data that is available at a particular time point, with no imputation for missing values. This data will be used primarily for safety analyses and for some analyses of efficacy.

7. TREATMENT COMPARISONS

7.1. Primary Comparison of Interest

No formal treatment comparisons will be performed in this study.

7.2. Data Display Treatment Descriptors

In data displays, treatment groups will be defined as shown in Table 3.

Table 3 Data Display Treatment Descriptors

Treatment Group	Descriptor
DTG	DTG plus 2 NRTIs (DTG 50 mg twice-daily with 2 NRTIs until 2 weeks after completing TB therapy, then DTG 50 mg once daily with 2 NRTIs)
EFV	EFV 600 mg once daily plus 2 NRTIs

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1. Multicenter Studies

Data will be summarized for all centers combined. Country will be treated as an exploratory subgroup for analyses of the primary efficacy endpoint as described in Section 8.3.

8.2. Other Strata and Covariates

The randomization is stratified by screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and screening CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3).

8.3. Examination of Subgroups

Certain summaries and analyses of antiviral response will use subgroups from the following list:

- Baseline plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL);
- Baseline CD4+ cell count (≤100 cells/mm^3 or >100 cells/mm^3);
- Race (White vs Non-White, African American/African heritage vs Non African American/African heritage)
- Gender (female or male);
- Age (<50 or ≥50);
- Country;

8.4. Multiplicity and multiple comparisons

No adjustments for multiplicity are required as no formal statistical hypothesis testing will be performed. No multiple comparisons will be performed.

8.5. Virology

Genotypic and phenotypic testing will be conducted for subjects meeting confirmed virologic withdrawal criteria, i.e., confirmed HIV-1 RNA ≥400 c/mL from Week 24 onwards. The samples from Day 1 and from the "suspected virologic withdrawal criterion" visit will be tested (i.e., the first of the two consecutive results ≥400 c/mL). Treatment-emergent genotypic and phenotypic resistance will be investigated for the Viral Genotypic/Phenotypic populations, respectively.

8.5.1. Genotype

An assessment will be made of every change across all amino acids within the IN encoding region at Day 1 and time of meeting confirmed withdrawal criteria, with particular attention paid to specific amino acid changes associated with the development

of resistance to RAL, EVG, or DTG. The known IN mutations associated with the development of resistance to RAL, EVG, or DTG are shown in Table 4.

Table 4 IN Mutations Associated with Development of Resistance to DTG

Known IN mutations associated with the development of resistance to RAL, EVG or DTG:

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A/I/K**, **E92Q/V**/G, Q95K, T97A, G118R, **F121Y**, E138A/K /T, G140A/C/S, **Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R**/N, **V151L**/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, S230R, R263K L68V/I,* L74I/M, * E138D,* V151I,* G193E *

Note: draft listing; may be modified in case of additional substantive data availability.

- INI mutations listed taken from Stanford HIV Resistance Database (http://hivdb.stanford.edu/DR/cgi-bin/rules_scores_hivdb.cgi?class=INI cited 03Feb2017) and accessed on 07Mar 2017.
- Each INI mutation listed had a score of ≥10. INI substitutions listed above in bold had a score of =60.

  * Denotes additional INI mutations added as they were identified during in vitro passage of DTG or seen in a previous DTG study in INI-experienced subjects (ING112574).

Major resistance mutations to other classes (i.e., NRTI, NNRTI, PI) as defined by the International Antiviral Society-USA (IAS-USA) and shown in Table 5 will be evaluated.

Table 5 Major Mutations Associated with Resistance to Other Classes

NRTIs	M41L, A62V, K65R/E/N, D67N, 69 insert, K70R/E, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E
NNRTIs	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I/L
PIs	D30N, V32I, M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M

Note: the most recent information available from IAS-USA (https://www.iasusa.org/content/essential-management-hiv-infection) will be used, should it be revised before the time of analysis. This table is based on January 2017 revisions.

8.5.2. Phenotype

Phenotypic susceptibility to all licensed antiretroviral drugs, including DTG and EFV, will be determined using PhenoSense HIV assays from Monogram Inc. and will be reported as fold change (FC) in IC_{50} relative to wild-type control virus NL4-3, i.e., FC of sample virus = IC_{50} of sample virus/IC_{50} of control virus. Since the maximum assay limit for FC for each ART varies from subject to subject, FC values that are greater than the maximum assay limit (e.g., '>100') will be interpreted as having a value equal to the smallest maximum assay limit for that ART in the study population for data analysis. Censored values will be presented 'as is' in the listings. Phenotypic susceptibilities will be categorised according to FC as shown in Table 6 (based on Monogram PhenoSense assay). Clinical cutoffs (where available) or biological cutoffs by PhenoSense will be used to define the phenotypic susceptibility of background treatment.

Replication capacity is generated as part of standard phenotypic assays.

Table 6 Clinical and Biological Cutoff Values for the PhenoSense HIV Drug Resistance Assay

Drug	Abbreviation	Class	PhenoSense cutoff
Abacavir	ABC	NRTI	(4.5 – 6.5)[a]
Lamivudine	3TC	NRTI	3.5 [a]
Didanosine	ddI	NRTI	(1.3 – 2.2) [a]
Stavudine	d4T	NRTI	1.7 [a]
Zidovudine	AZT (ZDV)	NRTI	1.9[b]
Emtricitabine	FTC	NRTI	3.5[b]
Tenofovir	TDF	NRTI	(1.4 – 4) [a]
Delavirdine	DLV	NNRTI	6.2[b]
Efavirenz	EFV	NNRTI	3[b]
Nevirapine	NVP	NNRTI	4.5[b]
Etravirine	ETR	NNRTI	(2.9 – 10)[a]
Rilpivirine	RPV	NNRTI	2[b]
Fosamprenavir/r	FPV/r	PI	(4 – 11) [a]
Atazanavir/r	ATV/r	PI	5.2 [a]
Indinavir/r	IDV/r	PI	10 [a]
Lopinavir/r	LPV/r	PI	(9 – 55) [a]
Nelfinavir	NFV	PI	3.6[b]
Saquinavir/r	SQV/r	PI	(2.3 – 12) [a]
Tipranavir/r	TPV/r	PI	(2 – 8) [a]
Darunavir/r	DRV/r	PI	(10 – 90) [a]
Raltegravir	RAL	INI	1.5[b]
Elvitegravir	ELV	INI	2.5 [b]
Dolutegravir	DTG	INI	(4 – 13)[a]

a. clinical cutoff (lower cutoff – higher cutoff)
b. biological cutoff

Clinical cutoffs (where available) or biological cutoffs by PhenoSense will be used to define the phenotypic susceptibility to each drug in a subject's background regimen.

Biological/Clinical Cutoff:

Fold Change	Interpretation
> clinical lower cut-off or biologic cut-off	resistance
≤ clinical lower cut-off or biologic cut-off	sensitive

Clinical Cutoff:

Fold Change	Interpretation
> clinical higher cut-off	resistance
≤ clinical higher cut-off and > clinical lower cut-off	partially sensitive
≤ clinical lower cut-off	sensitive

8.6. Combining Treatment Phases and States

On-treatment and Post-treatment assessments and events will be classified as occurring during the Randomized or OLE Phase of the study as follow:

- If a subject did not enter the OLE Phase, then any Post-treatment data will be assigned to the Randomized Phase.
- For subjects who did enter the OLE Phase, any Post-treatment data will be assigned to the OLE Phase.

8.7. Data Reporting

For Week 24 and 48 analyses, summary outputs will include all available data at the time of data cut from the Randomized Phase, unless otherwise stated. A few selected outputs will report all available data at the time of data cut from both Randomized and OLE phases. Output titles will denote the phase(s) that they report data from.

9. DATA HANDLING CONVENTIONS

All data manipulations, tabulations, calculations, and figures will be performed using SAS Version 9.1.3 or higher on a system of WINDOWS computers.

9.1. Premature Withdrawal and Missing Data

9.1.1. Methods for Proportion Endpoints Based on Plasma HIV-1 RNA - Snapshot

For each scheduled assessment time, the Snapshot response rate for a given threshold (e.g., <50 c/mL) is defined as:

$$\text{Snapshot Rate} = \frac{\text{Number of responders in that analysis window}}{\text{Number of subjects in the analysis population}}$$

In each analysis window, a subject is defined as a responder as per the algorithm described in Section 9.2.7. In particular, if no HIV-1 RNA assessment is available for a subject in the assessment window, then that subject will be counted as a non-responder. The nature of this missing data will be further classified in Snapshot summaries as either 'Virologic Failure' or 'No Virologic Data at Week X'; see Section 9.2.7 for full details.

9.1.2. Methods for Other Data

For other laboratory data (e.g., HIV-1 RNA as a continuous measure, CD4+ cell counts, haematology, and clinical chemistry) no imputation for missing data or premature discontinuation will be performed and the observed values will be used.

9.1.3. Methods for Missing Dates

9.1.3.1. Date of Birth

Due to local privacy regulations, only the year of birth is recorded in the eCRF. The following algorithm will be used for imputation:

- All dates of birth will be imputed using the 30th day of June.

Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.

In listings of demographic data, the year of birth as entered will be displayed.

9.1.3.2. Adverse Events

The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:

- For a missing start day, the 1st of the month will be used unless this is on the same month but before the start date of investigational product; in this case the IP start date will be used (and hence the event is considered On-treatment as per Section 9.3.1).
- For a missing stop day, the last day of the month (28th, 29th, 30th, or 31st as appropriate for the month and year) will be used, unless this is on the same month but after the stop date of IP; in this case the IP stop date will be used.

Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

In listings of AE data, the partial start and end dates as entered will be displayed.

9.1.3.3. Concomitant Medications

Missing dates for concomitant medications (including TB medication)/ARTs are handled as described in Section 9.3.5.

9.1.3.4. Exposure

If a partial or a missing IP stop date is recorded in the eCRF while study is ongoing, the following convention will be used:

- if an IP stop date is partial where the day is missing (i.e., MMMYYYY), the last day of the month (28/29/30/31 depending on the month and year), the date of last visit, or the recorded date of withdrawal/completion, whichever is earlier, will be used.
- if an IP stop date is partial where the day and month are missing, the last day of the year i.e., 31DECYYYY, the date of last visit, or the recorded date of withdrawal/completion, whichever is earlier, will be used.

- if an IP stop date is completely missing, the date of last visit or the recorded date of withdrawal/completion, whichever is earlier, will be used.

9.2. Derived and Transformed Data

9.2.1. Age

Age, in whole years, will be calculated with respect to the subject's Screening visit. Only subjects' year of birth is recorded in the eCRF, hence the imputed date of birth (see Section 9.1.3.1) will be used to calculate the subject's age.

9.2.2. Baseline and Change from Baseline

Unless stated otherwise, the baseline value for a parameter (including labs, vital signs, virology assessments, etc.) is defined as the last Pre-treatment (see Section 9.3.1) value observed. This is generally expected to be from the Day 1 visit, although such values may be missing or unscheduled assessments may be performed before treatment start. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.

Change from baseline for a parameter is calculated as (observed value - baseline value).

The percentage change from baseline for a parameter is calculated as

$$\%\ \text{change from baseline} = \frac{\text{observed value} - \text{baseline value}}{\text{baseline value}} \times 100$$

9.2.3. Exposure

A subject's exposure, in days, to investigational product will be calculated as

Exposure = IP Stop Date – IP Start Date + 1

where IP Stop Date is the date of final dose of IP received and IP Start Date is the date of initial dose of IP in the study. If IP Stop Date is partial or missing it will be imputed as Section 9.1.3.4.

An alternative calculation of exposure will be performed where the duration of any dosing interruptions, based on eCRF data, will be subtracted from the result above.

9.2.4. Framingham Risk Equation

The predicted probability, $\hat{p}$, of having a cardiovascular disease (CVD) within the next 10-years according to the Framingham formula [D'Agostino et al., 2008] is:

for females:

$$\hat{p}_F = 1 - S_0(t)^{\exp\{\ 2.32888 \times \log(\text{age}) + 1.20904 \times \log(TC) - 0.70833 \times \log(HDL) + 2.76157 \times \log(SBPu) + 2.82263 \times \log(SBPt) + 0.52873 \times I_s + 0.69154 \times I_d - 26.1931\}},$$

for males:

$$\hat{p}_M = 1 - S_0(t)^{\exp\{\ 3.06117 \times \log(\text{age}) + 1.12370 \times \log(TC) - 0.93263 \times \log(HDL) + 1.93303 \times \log(SBPu) + 1.99881 \times \log(SBPt) + 0.65451 \times I_s + 0.57367 \times I_d - 23.9802\}},$$

where

$$S_0(t) = \begin{cases} 0.95012, \text{females} \\ 0.88936, \text{males} \end{cases}$$

TC = total serum cholesterol (mg/dL),
HDL = serum HDL cholesterol (mg/dL),
$SBPu$ = systolic blood pressure (mmHg) if subject is not treated for high blood pressure (note that if a subject is treated for high blood pressure then log($SBPu$) = 0)
$SBPt$ = systolic blood pressure (mmHg) if subject is treated for high blood pressure (note that if a subject is not treated for high blood pressure then log($SBPt$) = 0)

$$I_s = \begin{cases} 1, \textit{current smoker} \\ 0, \textit{otherwise} \end{cases}$$

$$I_d = \begin{cases} 1, \textit{diabetic} \\ 0, \textit{otherwise} \end{cases}$$

A subject will be considered as treated for high blood pressure if during screening it has specified that is suffering from hypertension.

A subject is classified as diabetic if current or past is indicated in the medical conditions eCRF for Type 1 or Type 2 diabetes mellitus, or if baseline fasting glucose ≥7.00 mmol/L (126 mg/dL).

Smoking status is collected in the eCRF on Day 1. A current smoker is defined as currently smoking/using tobacco or has smoked/used tobacco within the previous 6 months; a former smoker is defined as previously smoked/used tobacco products and has not smoked/used tobacco products within the previous 6 months.

This calculation will not be performed for subjects who have indicated current or past myocardial infarction conditions on the eCRF. These subjects will not be included in summary statistics of risk, but will be counted in the highest category of risk (≥20%) in the summary by category.

9.2.5. Genotype

A mutation is considered present whenever the encoded amino acid residue differs from the amino acid that would have been encoded by the wild-type (e.g., HXB2, NL43) comparator gene; e.g., Q148K. If the encoded amino acid is seen as a mixture of wild-type and mutant amino acid, e.g., Q148Q/K, the mutated amino acid is considered present at the codon of interest. If the encoded amino acid is seen as a mixture of two or more amino acids, which may or may not include wild type, e.g., Q148K/H or Q148K/H/Q, etc., for the purposes of calculating the number of mutated amino acids, only one mutation is considered to be present at the codon of interest.

Table 7 shows how different amino acid changes will be represented.

Table 7 Representation of Amino Acid Changes

Mutations	Amino acid change
T69S	Single mutation from amino acid 'T' (vendor reference) to 'S' (sample) at codon '69'
Q148H/K/R	Mixture of amino acid mutations 'H', 'K' and 'R' (sample) from amino acid 'Q' (vendor reference) at codon '148'
_69_1T	First insertion of amino acid 'T' (sample) at codon '69'
_69_2S	Second insertion of amino acid 'S' (sample) at codon '69'
_69_3S/A	Third insertion of a mixture of amino acids 'S' and 'A' (sample) at codon '69'
L74L/-	Mixture of amino acid 'L' (sample) and a deletion at codon '74'
V75-	Single deletion of amino acid (sample) at codon '75'

9.2.6. Hepatitis Status

Hepatitis C status will be determined using antibody (IgM or IgG) and/or hepatitis C virus (HCV) RNA. If both antibody and virus RNA assessments are available, the latter will take precedence and positive/negative status will be based on whether HCV RNA is detectable (i.e., ≥43 IU/mL [≥1.63 log IU/mL]) or not.

A subject will be considered positive for hepatitis B virus (HBV) if they have a positive surface antigen or detectable HBV DNA. Although Subject with hepatitis B are excluded from the study, subjects meeting liver stopping criterion will be tested for Hepatitis B, and incident new hepatitis B infection will be summarised.

Baseline hepatitis status will be based on Pre-treatment laboratory assessments.

9.2.7. Modified Snapshot Algorithm

The FDA Snapshot algorithm is intended to be primarily a virologic assessment of the endpoint, and as such follows a "virology first" hierarchy.

Virologic Success (e.g., <50 c/mL) or Virologic Failure within an analysis window (see Section 9.3.2) is typically determined by the last available HIV-1 RNA measurement in that window while the subject is On-treatment.

When no HIV-1 RNA data is available within a window, a subject cannot be a Virologic Success. Depending on the reason for lack of data, the subject will be classified as a Virologic Failure or reported as 'No Virologic Data at Week X'; in the latter case, the algorithm further classifies the nature of the missing data. Typically, a subject withdrawn (i) due to AE or, (ii) for another reason yet was suppressed at the time (i.e., last available HIV-1 RNA <50 c/mL), will be counted as 'No Virologic Data at Week X'. Should a subject withdraw for reasons other than AE and was not suppressed at the time, they will be a Virologic Failure.

A single switch of background NRTI therapy to an alternate approved NRTI therapy for toxicity or tolerability management is not considered as Virologic Failure at any time regardless of viral load at the time of switch. A subject would be considered to be a Virologic Failure if they make other changes to their ART regimen (e.g., addition of

other ARTs to the study-specified regimens, or non-permitted switches in background NRTI). This includes:

- A substitution of or switch between DTG or EFV
- Switch of background NRTI therapy to an alternate approved NRTI therapy for toxicity or tolerability management more than one time
- Switches of a background NRTI for any reason other than toxicity or tolerability

Full details of the algorithm, including the handling of special cases, are included in Section 17.3.

9.2.8. National Cholesterol Education Program (NCEP) Lipid Categories

In addition to DAIDS toxicity scales (see ING117175 protocol, Appendix 3, Section 11.3), lipid values will be categorized according to the 2001 NCEP Adult Lipid Guidelines [Grundy, 2001] shown in Table 8.

Table 8 NCEP Lipid Categories

Parameter	Value Range (mmol/L)	Value Range (mg/dL)	Category
Triglycerides	<1.70	<150	Normal
	1.70 to <2.26	150 to <200	Borderline High
	2.26 to <5.65	200 to <500	High
	≥5.65	≥500	Very High
Total Cholesterol	<5.18	<200	Desirable
	5.18 to <6.21	200 to <240	Borderline High
	≥6.21	≥240	High
HDL Cholesterol	<1.04	<40	Low
	1.04 to <1.56	40 to <60	Normal
	≥1.56	≥60	High
LDL Cholesterol	<2.59	<100	Optimal
	2.59 to <3.37	100 to <130	Near/Above Optimal
	3.37 to <4.14	130 to <160	Borderline High
	4.14 to <4.92	160 to <190	High
	≥4.92	≥190	Very High

9.2.9. Plasma HIV-1 RNA

For summaries and analyses which use HIV-1 RNA level as a continuous measure, the logarithm to base 10 of the value will be used.

HIV-1 RNA results may be provided as censored values, such as <40 or >9,999,999 c/mL. For the purposes of summary statistics, such values will be replaced by the next value beyond the limit of detection, e.g., 39 or 10,000,000 c/mL, respectively, for the given examples. Data listings will show the censored values as provided.

In addition, HIV-1 RNA results including whether "Target Detected" or "Target Not Detected" for values <40 c/mL will also be presented in a listing.

9.2.10. CD4+ Cell Counts

CD4+ values provided as non-numeric, censored results from the central laboratory e.g., '<0.02' in original units of GI/L will be imputed as 0.019 and '≤0.02' in original units of GI/L will be imputed as 0.02 so that they are converted to standard units of cells/mm^3 and included in the CD4 summary statistics. The listing will report the censored result as '<20' in the standard units, i.e., equivalent to <0.02 GI/L.

9.2.11. Lab Toxicities

Toxicities will be based on the Division of AIDS (DAIDS) grading system, as specified in the protocol. Toxicity grades provided by the central laboratory do not distinguish between abnormally high or low criteria, when both are relevant for a particular parameter. When summarising toxicity grades for such parameters, they will be categorized as in Table 9 according to whether they are above or below the midpoint of normal range.

Table 9 Categorization of Select Lab Parameters Relative to Midpoint of Normal Range

Parameter	Below Midpoint	Above Midpoint
Fasted glucose	Hypoglycaemia	Hyperglycaemia
Sodium	Hyponatremia	Hypernatremia
Potassium	Hypokalemia	Hyperkalemia

9.2.12. TB Treatment Success

The current definitions of TB treatment outcomes (using the WHO definition [WHO, 2014]) can be defined in 6 categories:

- **Cure** – A pulmonary TB subject with bacteriologically confirmed TB at the beginning of the treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. A pleural only TB or lymph node (LN) only TB subject will not comply with this outcome.
- **Treatment completed** – A TB subject who completed treatment (defined below) without evidence of failure BUT with no record to show that sputum smear or culture result in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
- **Treatment failed** – A TB subject whose sputum smear or culture is positive at 5 months or later during treatment.
- **Died** – A TB subject who dies for any reason before starting or during the course of treatment.
- **Lost to follow-up** – A TB subject who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

- **Not evaluated** – A TB subject for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Treatment success is when TB treatment outcome is either Cure or Treatment Completed.

Subjects diagnosed with RIF resistant-TB of multidrug resistant-TB, who are placed on a second-line regimen will be excluded from this analysis.

Note that a subject who has multiple TB infections with pulmonary TB will be considered as pulmonary TB subject.

Completion of treatment will be satisfied if all the doses planned for the initial phase be taken within 3 months and those for the continuation phase (4 or 7 months, according to local guidelines) be taken within the planned period plus 3 months (7 or 10 months).

9.2.13. Study Day

The Study Day of an event (e.g., lab assessment, vital sign, and start date of AE or HIV associated condition) will be derived as the number of days between the date of the event and the initial start date of IP as follows:

1. if date of event ≥ start date of IP, then

$$\text{Study Day} = \text{Date of Event} - \text{Start Date of IP} + 1$$

2. if date of event < start date of IP, then

$$\text{Study Day} = \text{Date of Event} - \text{Start Date of IP}$$

Note that the initial start date of IP is considered to be on Study Day 1 and the day before this is Study Day -1; i.e., there is no Study Day 0.

9.2.14. Total Cholesterol / HDL Cholesterol Ratio

When both total cholesterol and HDL cholesterol results are available from the same date for a subject, then the ratio will be calculated by dividing the total cholesterol result by the HDL cholesterol result. The ratio can be classified as follows:

Parameter	Value Range
Total Cholesterol / HDL Ratio	< 3.5
	3.5 to < 4.4
	4.4 to < 5
	≥ 5

9.3. Assessment Windows

9.3.1. Study Phase and Treatment State

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of IP as either Pre-treatment, On-treatment or Post-treatment.

For laboratory data, HIV and TB associated conditions, vital signs, and genotypic and phenotypic data, treatment state will be defined as in Table 10.

Table 10 Treatment State for Laboratory Data, HIV Associated Conditions, Vital Signs, and Genotypic and Phenotypic Data

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
Randomized Phase (Day 1 – Week 48 plus 4-Week Extension)	Pre-Treatment	date ≤ IP Start Date
	On-Treatment	IP Start Date < date ≤ Week 52 Date of Visit (DOV)
		or if withdrawn prior to or at Week 52: IP Start Date < date ≤ IP Stop Date + 1
	Post-Treatment (withdrawn prior to Week 52 or not enter the Extension)	date > IP Stop Date + 1
Extension	On-treatment	Week 52 DOV < date ≤ IP Stop Date +1
	Post-Treatment	date > IP Stop Date + 1

If the IP Stop Date for any study phase is completely missing, then any assessment after that IP Start Date will be considered to be On-treatment for that study phase.

For adverse events, treatment state will be defined as in Table 11, where a partial AE start date uses imputation as described in Section 9.1.3.2. In the case of a completely missing start date, the event will be considered to have started On-treatment unless an end date for the AE is provided which is before start of investigational product; in such a case the AE is assigned as Pre-treatment.

Table 11 Treatment State for Adverse Events

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
Randomized Phase (Day 1 – Week 48 plus 4-Week Extension)	Pre-Treatment	date < IP Start Date
	On-Treatment	IP Start Date ≤ date ≤ Week 52 Date of Visit (DOV)
		or if withdrawn prior to Week 52: IP Start Date ≤ date ≤ IP Stop Date
	Post-Treatment (withdrawn prior to Week 52 or not enter the DTG Open-Label Extension)	date > IP Stop Date

Study Phase	Treatment State	Assessment/Start Date vs. IP Start/Stop Date
Extension	On-treatment	Week 52 DOV < date ≤ IP Stop Date
	Post-Treatment	date > IP Stop Date

If the IP Stop Date for any study phase is completely missing, then any event with a start date on or after IP Start Date will be considered to be On-treatment for that study phase. If the start date of the AE for any study phase is after IP Stop Date for that study phase but has been recorded as potentially related to IP, then it will be classified as On-treatment for that study phase.

For reporting purposes, prior, concomitant, and follow-up medications will be classified according to treatment states defined in Section 9.3.5.

9.3.2. Assessment Window Assignment

Withdrawal date from IP/investigational product, laboratory data, vital signs, and genotypic and phenotypic data will be assigned to assessment windows according to actual dates rather than the nominal visit labels as recorded on the eCRF or in the laboratory database.

A window around a target Study Day will typically include all days from the midpoints between it and the target Study Days of the previous and the proceeding visits. In general, the nominal target study day for week w is $(7*w)+1$.

Based on the Study Day (see Section 9.2.13), assessments are assigned as shown in Table 12 for modified Snapshot, and in Table 13 for all other endpoints.

Table 12 Modified Snapshot Assessment Windows

Study Day of Assessment	Assessment Window	Target Study Day of Window
≤-4	Screen	-28
-3 to 1	Day 1	1
2 to 42	Week 4	29
43 to 70	Week 8	57
71 to 126	Week 12	85
127 to 210	Week 24	169
211 to 294	Week 36	253
295 to 378	Week 48	337

Table 13 Assessment Windows for all other endpoints

Study Day of Assessment	Assessment Window	Target Study Day of Window
≤-4	Screen	-28
-3 to 1	Day 1	1
2 to 42	Week 4	29
43 to 70	Week 8	57
71 to 126	Week 12	85
127 to 210	Week 24	169
211 to 294	Week 36	253
295 to 350	Week 48	337
351 to 392	Week 52	365
393 to 462	Week 60	421
(7*w - 41) to (7*w + 42) (Only those subjects randomized to receive DTG plus 2 NRTIs will enter into the extension phase)	Week w w =72, 84, 96,…	7*w + 1
> (Study Day of last dose + 1)	Follow-up	Study Day of last dose + 28

Note for key efficacy time points at Week 24 and Week 48 that the windows have been defined to cover ± 6 weeks, regardless of the midpoint between adjacent target Study Days. The windows for the adjacent periods are adjusted accordingly.

For parameters which are not scheduled to be assessed at particular visits, the all-inclusive windows defined in Table 12 will still be used; however, data summaries will only report scheduled visits. Assessments at unscheduled visits will be included for 'any time On-treatment' time points and in data listings, as well any algorithms that make use of additional data (e.g., Snapshot).

9.3.3. Multiple Assessments

If after window assignment there are multiple valid (see Section 9.3.2) assessments of a parameter within the same window and associated with the scheduled Study Phase, then the following hierarchy will be used to determine the value to be used for summary statistics of observed values:

1. the assessment closest to the window target Study Day;
2. if there are multiple assessments equidistant from the target Study Day, then for continuous variables the mean of these values will be used and for categorical variables the worst value. For HIV-1 RNA, the geometric mean of the number of copies will be used as opposed to the arithmetic mean.

Assessments not chosen for use in summary statistics by this algorithm will still appear in the associated listings. Also, such valid assessments will be used when determining values of potential clinical concern for the 'any time On-treatment' time point, and for any algorithm that has specific rules for which observation to use (e.g., Snapshot).

9.3.4. Invalid Laboratory Assessments

Certain laboratory endpoints are required to be collected in a fasting state, i.e., glucose and lipids (triglycerides, total cholesterol, HDL, LDL). If these endpoints are collected in a non-fasting state, then the results will be excluded from summaries; such results will be included in data listings with the fasting status noted.

9.3.5. Classification of Prior, Concomitant, and Post-Therapy Medications

Prior medications are those taken (i.e., started) before the start date of Investigational product. Concomitant medications are those taken (i.e., started or continued) at any time between the start date and stop date of IP, inclusive. Prior medications that were continued during this period are also considered as concomitant medications. Post-treatment medications are those started after the stop date of IP. Concomitant medications that were continued during this period are also considered as post-treatment medications.

It will be assumed that medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as IP, it will be assumed that the medication was taken after the subject started taking IP.

Table 14 illustrates how a medication is classified as prior, concomitant, or post-treatment.

Table 14 Prior, Concomitant, and Post-treatment Classification of Medications

	Pre-treatment	On-treatment			Post-treatment		Prior	Conco-mitant	Post
		IP Start Date		IP Stop Date	IP Stop Date+1				
(a)	x————x						Y	N	N
(b)	x————		————x				Y	Y	N
(c)	x————		————			————x	Y	Y	Y
(d)			x————x				N	Y	N
(e)			x————			————x	N	Y	Y
(f)						x————x	N	N	Y
(g)	?————x						Y	N	N
(h)	?————		————x				Y*	Y	N
(i)	?————		————			————x	Y*	Y*	Y
(j)	x————		————			————?	Y	Y**	Y**
(k)			x————			————?	N	Y	Y**
(l)						x————?	N	N	Y
(m)	?————		————			————?	Y***	Y***	Y***
(n)	x————	x					Y	Y	N
(o)	?————	x					Y*	Y	N
(p)		x	————x				N	Y	N
(q)		x	————	x			N	Y	N
(r)				x	—	————x	N	Y	Y
(s)				x	—	————?	N	Y	Y**
(t)					x	————x	N	N	Y
(u)					x	————?	N	N	Y
(v)			x————	—	x		N	Y	Y

x = start/stop date of medication
? = missing start/stop date of medication
* If a medication is stopped On-treatment or Post-treatment and no start date is recorded it will be assumed that the medication was ongoing from the Pre-treatment phase
** If a medication is started Pre-treatment or On-treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-treatment phase to the Post-treatment phase

If a partial date is recorded in the eCRF, the following convention will be used to assign the medication:

- if the partial date is a start date, a '01' will be used for missing days and 'Jan' will be used for missing months;
- if the partial date is a stop date, a '28/29/30/31' will be used for the missing day (dependent on the month and year) and 'Dec' will be used for missing months; for medications recorded in the eCRF as prior ART, the earlier of this imputed date or the day before IP start will be used.

The recorded partial date will be displayed in listings.

9.3.6. Post-baseline

Post-baseline refers to the combined time periods of On-treatment and Post-treatment (Section 9.3.1).

9.4. Values of Potential Clinical Importance

The DAIDS grading for severity of laboratory toxicities and clinical adverse events is included in the protocol (Appendix 3, Section 11.3). The central laboratory will flag lab parameter toxicities directly in the provided datasets.

10. STUDY POPULATION

All displays referred to in this section will be presented for the ITT-E population using the treatment groups in Table 3, unless otherwise indicated.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

10.1. Disposition of Subjects

The total number of subjects in each analysis population will be summarized and a listing will present which populations each screened subject belongs to. The number and percentage of subjects who failed screening will be summarized by reason for failure, and a listing of reasons for each screen failure subject will be produced. The number of subjects enrolled will be summarized by country and investigator.

A listing will be produced to show any subjects randomized but who did not receive IP, along with the reason for discontinuation at this stage.

Treatment assignment (or none, if failed screening) will be listed by country and site number for all screened subjects. For randomized subjects, a listing will be produced showing the randomized and actual strata, treatment assignments, and start date of IP; any deviations between randomized and actual strata values will be flagged, and this listing will also be ordered by country and site number.

A listing of each subject's study visit dates by country and site will be produced. This listing will indicate study phase (Section 9.3.1), the treatment state (Section 9.3.1) and assessment window (Section 9.3.2) the visit was assigned to.

A summary of subject disposition, i.e., the number and percentage of subjects who completed (as defined in the protocol) or withdrew from the study as recorded in the eCRF Study Conclusion page, will be produced. This summary will also include the primary and any sub-reasons for withdrawal. Subjects who have not been recorded as either completing or withdrawing from the study will be categorized as "Ongoing at time of the analysis" for summary purposes. A listing of reasons for subjects who withdrew from the study will be provided.

The subject disposition will also be summarized separately by study phase i.e., Randomized Phase and Open-Label Extension Phase.

In addition, a summary of subject disposition by visit will be presented. The number of subjects On-treatment at each scheduled visit will be given along with the number and percentage of subjects who withdrew from the study before the next scheduled visit. This display will include the subject numbers and reason(s) for withdrawal.

10.2. Protocol Deviations

10.2.1. Inclusion / Exclusion Criteria

The number and percentage of subjects who deviated from inclusion or exclusion criteria will be summarized. A listing of subjects and the criteria they deviated from will be produced.

10.2.2. Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial. Important protocol deviations reported in the study will be reviewed by a cross-functional team on a monthly basis and may include categories listed below:

- Informed consent procedure deviation (e.g., no informed consent signed prior to any screening procedure)
- Eligibility criteria deviation (e.g., any inclusion criteria not met or exclusion criteria met)
- Withdrawal criteria deviation (e.g., subject met study withdrawal criteria but was not withdrawn)
- Prohibited medication deviation (e.g., subject received any medications that may cause decreased concentrations of DTG during the study)
- IP administration deviation (e.g., treatment received not as randomized)
- Assessment procedure deviation (e.g., missing baseline assessments that affect endpoint evaluation)

All important protocol deviations based on protocol deviation rules document (See PD Rules document) will be summarized and listed for Week 24 and Week 48 analyses.

A summary of protocol deviations leading to discontinuation from the PP population will be produced.

10.2.3. Protocol Deviations Leading to Exclusion from the Per-Protocol Population

Protocol deviations leading to exclusion from the PP population are those deviations which may

i. directly impact the efficacy endpoint of HIV-1 RNA; or

ii. lead to permanent discontinuation of IP/withdrawal and hence indirectly impact the efficacy endpoint by causing data to be missing.

The following criteria define the protocol deviations which, if they occur prior to an analysis time point of interest, will lead to exclusion of a subject from the Per-Protocol population for that analysis. Potential protocol deviations leading to exclusion from PP population will be reviewed by the study team to confirm that they meet these criteria. This review will occur before the clinical database has been frozen for analysis. The review process will be conducted for Week 24 and Week 48 analysis.

- Subject deviates from any inclusion or exclusion criteria, as recorded in the eCRF;
- Subject took/received incorrect IP, i.e., other than the one to which they were randomized for greater than 10% of the total time On-treatment;
- Interruption of IP for greater than 10% of the total time On-treatment, for reasons other than treatment-related adverse events/laboratory abnormalities, based on eCRF IP exposure forms;
- Prohibited medications: receiving ART medication other than that prescribed/allowed by the study for a duration of >2 consecutive weeks or receiving non-ART medication that would impact exposure or response to therapy with duration taken into consideration. Clinical/the study physician will review the listing of unique concomitant medication terms on a regular basis before database freeze and identify the prohibited medications (with duration as appropriate for non-ARTs);
- Permanent discontinuation of IP/withdrawal due to a reason of "Protocol Deviation" (as recorded in the eCRF).

The final determination of protocol deviations leading to exclusion from per-protocol population will be made prior to database freeze.

The number and percentage of subjects with protocol deviations leading to exclusion from the Per-Protocol population will be summarized. A listing of subjects and such protocol deviations will be produced.

10.3. Demographic and Baseline Characteristics

Demographic characteristics (gender, age, ethnicity, weight and height) collected at screening (Day 1 for weight and height) will be summarized. Year of birth, screening assessment date and the demographic characteristics will be listed for each subject.

The five high level FDA race categories and designated Asian subcategories will be summarized along with all combinations of high level categories which exist in the data. The nine race categories collected will be summarized along with categories for mixed race. A by-subject listing of race will also be produced.

Hepatitis B and C status at entry will be summarized and all Hepatitis B and C results will be listed.

Tuberculosis diagnosis by smear, culture, and nucleic acid amplification methods, as well as rifampicin susceptibility documented results, at entry will be listed. The planned duration of TB treatment recorded in the eCRF and the actual duration of TB treatment calculating from start date to stop date excluding any treatment interruptions (not counting treatment changes [Bridging regimen as defined in the protocol] as interruptions) will be summarized.

Numbers and percentages of subjects with CDC Classification of HIV Infection, categories A, B, and C, at baseline will be summarized and listed.

Current and past medical conditions at Day 1 will be summarized separately. Certain categories (cardiac, gastrointestinal, metabolism and nutrition, psychiatric, renal and urinary, and nervous system) will be summarized again to include the specific sub-conditions which were also collected. TB diagnoses (pulmonary, pleural, and lymph node tuberculosis) collected under medical condition of special interest will also be separately summarized. All past and current medical conditions will be listed for all subjects. A separate medical condition listing will be generated for Mexican subjects who had an adverse event at study closeout. Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A summary of cardiovascular risk assessments at Day 1 will be produced. The number and percentages of subjects with a family history of cardiovascular risk, subjects' smoking history and use of illicit drugs, and subjects' history of cardiac surgery procedures will be provided. The summary will also include a 10-year risk of coronary heart disease, as calculated using Baseline values in the Framingham equation (see Section 9.2.4); summary statistics will be presented along with the number and percentage of subjects with <10%, 10% to <20%, and ≥20% risk. Listings of data related to cardiovascular risk assessments will be produced.

The distribution of CD4+ cell count data (cells/mm^3) and plasma HIV-1 RNA (c/mL) at Screening and Baseline will be summarized. This will include the number and percentage of subjects in the categories specified in Section 8.3, as well as summary statistics of cells/mm^3 and log_{10} c/mL values, respectively. A listing of HIV-1 RNA and CD4+ values will be included in efficacy outputs.

10.4. Dispensing Information

A listing of dispensation information for IP (dates and number of tablets dispensed and returned) will be produced.

10.5. Concomitant Medications

For reporting purposes, medications will be classified as prior, concomitant, and/or post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of investigational product (see Section 9.3.5). Medications will be coded using the GSK Drug coding dictionary.

Concomitant medications will be summarized by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1 (body system). Drugs will be displayed according

to the ATC classifications of both their ingredient and combination term. The data will also be summarized by ingredient combinations alone.

TB treatment medications with dose, start and stop dates will be separately summarized (by ingredient term) and listed.

A summary of the number and percentage of subjects receiving concomitant medications will also be displayed using a method that presents multi-ingredient medications according to their combination ATC classification rather than the classifications of the ingredients. This display will also include single-ingredient medications. Multi-ingredient medications will be labelled according to the sum of their ingredients, e.g., "TYLENOL Cold and Flu" would appear as "CHLORPHENAMINE MALEATE + DEXTROMETHORPHAN HYDROBROMIDE + PARACETAMOL + PSEUDOEPHEDRINE HYDROCHLORIDE" under the ATC headings for "Nervous System" and "Respiratory System" (the combination's ATC classifications).

Listings of all medications taken by subjects, including any which are only prior or post-treatment, will be produced for all subjects. At study closeout, a repeat listing will be provided for Mexican subjects who had an adverse event. The relationship between ATC level 1, ingredients and verbatim text for all medications in the study will be listed.

10.6. Prior and Concomitant ART

ART medications will also be classified as prior, concomitant, and/or post-treatment according to Section 9.3.5, with the following modifications:

- ART starting on IP stop date will be considered as only post-treatment and not concomitant. It is expected that after discontinuation of IP, a subject may immediately begin taking another ART.
- ART stopping on IP start date will only be considered as prior and not concomitant.
- any ART entered on the Prior ART eCRF with partial end date will be assumed to have finished before Screening.

Summaries of ART will be grouped by GSK Drug ATC classification level 4 (which will provide ART class). Classes are INI, NRTI, NNRTI, PI and Other. LAMIVUDINE should be grouped into NRTI.

Concomitant ART and median time between start of TB therapy and ART at time of IP start (i.e., the selected background dual NRTI) will be summarized. A listing will be produced for subjects who switch background therapy during the study.

Prior ART, concomitant ART, and post-treatment ART will be listed. Concomitant ART for Mexican subjects who had an adverse event will be presented in a separate listing at study closeout.

The relationship between ATC level 4, combination terms, and verbatim text will be listed.

11. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT-E population, unless stated otherwise.

Listings will present all available data, including from later phases which will not be summarized until future study reports. Listings will be grouped by the treatment groups of Table 3.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

11.1. Primary Efficacy Analysis: Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 in the DTG arm

The primary efficacy endpoint is the proportion of subjects in the DTG arm with HIV-1 RNA <50 c/mL at Week 48 using the modified Snapshot algorithm (see Section 9.2.7).

11.1.1. Summaries

The number and proportion of subjects with 95% CI with plasma HIV-1 RNA <50 c/mL based on the modified Snapshot algorithm at each visit by treatment group, will be presented with focus on the DTG arm at Week 48 as the primary endpoint of the study.

A summary of study outcomes (i.e., response below 50 c/mL, virologic failure or reason for no data in the window) at the time of analysis (Week 48), based on the modified Snapshot algorithm, will also be presented by treatment group.

11.1.2. Listings

Study outcomes will be listed.

Quantitative plasma HIV-1 RNA data will be listed including the interpretation of whether the virus is detected or not ('Detected' or 'Not Detected') by the assay.

11.1.3. Figures

The proportion of subjects with HIV-1 RNA <50 c/mL by visit based on the modified Snapshot algorithm and the individual plasma HIV-1 RNA profiles by visit will be graphically presented.

11.1.4. Supportive Analyses

11.1.4.1. Per Protocol Analysis

To assess the impact of major protocol deviations, the primary analysis described above will be performed using the Per-protocol population and the results will be compared for consistency with the results from the ITT-E population.

11.1.4.2. Exploration of Subgroups

A summary for the subgroups listed in Section 8.3 will be performed, showing the proportion of responders by treatment and subgroup.

11.1.4.3. Sensitivity analyses

Sensitivity analyses on MITT-E will be performed for an additional evaluation of the Week 24 snapshot and of the Week 48 primary endpoints.

11.2. Secondary Efficacy Analyses

11.2.1. Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the modified Snapshot algorithm

The proportion of subjects with Plasma HIV-1 RNA <50 c/mL based on the modified Snapshot algorithm at visits will be presented by treatment group, with focus on Week 24 as a secondary endpoint of the study.

Proportions at Week 24 will also be summarized by the subgroups of Section 8.3. Snapshot outcomes at Week 24 will be summarized by treatment group and listed.

The summaries will also be performed using MITT-E and Per Protocol populations.

11.2.2. Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the modified Snapshot algorithm in the EFV arm

The proportion of subjects with Plasma HIV-1 RNA <50 c/mL in the EFV arm based on the modified Snapshot algorithm will be summarized in the same manner as discussed in Section 11.1.

11.2.3. Time to Meeting Confirmed Virologic Withdrawal Criteria or Treatment Related Discontinuation

The distribution of time to meeting confirmed virologic withdrawal criteria (see ING117175 protocol, Section 4.6) or treatment related discontinuation will be estimated using the Kaplan-Meier nonparametric method by treatment group. This analysis will be performed using the TRDF data (as defined in Section 6.2.2).

The estimated proportion of subjects not meeting confirmed virologic withdrawal criteria nor discontinued due to treatment related reasons at the time of analysis at Week 24 (through Day 210) and Week 48 (through Day 350) will be presented by treatment group. This sensitivity analysis will be used to explore the impact of censoring subjects who have withdrawn for reasons not related to treatment; as this is an open-label study, there is a potential for withdrawal bias associated with the randomized treatment assignment.

Subjects who meet confirmed virologic withdrawal criteria will be listed, and a table which summarizes the simple proportion subjects meeting confirmed virologic withdrawal criteria will be provided by visit. The distribution of quantitative plasma

HIV-1 RNA results at the time of meeting suspected and confirmation of virologic withdrawal criteria will be summarized by treatment group.

11.2.4. Absolute Values and Changes from baseline in CD4+ counts at Week 24 and Week 48

The absolute values of CD4+ cell count (cells/mm^3) and the changes from baseline in CD4+ cell count (cells/mm^3) will be summarized by visit using ITT-E population, with focus on Week 24 and Week 48 as secondary endpoints of the study. The absolute values (i.e., observed values) and change from baseline CD4+ values (in cells/mm^3 and percentage of lymphocytes) will be listed.

11.3. Tertiary Efficacy Analyses

11.3.1. Incidence of disease progression (HIV-associated conditions, new AIDS diagnoses, and death)

11.3.1.1. HIV Associated Conditions

A summary of the number and percentage of all Post-baseline HIV associated conditions, including those which are a recurrence of a previous condition, will be presented. A summary excluding recurrences will also be provided. All data will be included in a listing.

11.3.1.2. HIV Disease Progression

The number and proportion of subjects experiencing clinical disease progression or death during the Post-baseline period will be presented, with clinical disease progression defined as the progression from baseline HIV disease status as follows:

- CDC Category A at baseline to CDC Category B event
- CDC Category A at baseline to CDC Category C event
- CDC Category B at baseline to CDC Category C event
- CDC Category C at baseline to new CDC Category C event
- CDC Category A, B or C at baseline to death

11.3.2. Proportion of subjects with TB treatment success (using the WHO definition)

The criteria for treatment success (TB treatment outcomes) as described in Section 9.2.12 will be summarized. Cure and treatment failed derivation will be based on culture results regardless of media and testing laboratory. The culture results at month 2 regardless of type of medium will be summarized as well. In addition, the sputum smear or culture result (solid medium and regardless of performing laboratory before and after TB treatment start) outcomes also will be summarized at 2 months.A similar summary will be performed for the liquid medium results. The results on solid medium and liquid medium will be summarized separately. A summary of proportion of subjects with TB

treatment success by treatment group will be presented. All outcomes will also be included in a listing.

11.3.3. Proportion of subjects with pulmonary tuberculosis who are sputum culture-negative 2 months after starting TB treatment

A summary of proportion of subjects with pulmonary tuberculosis as determined by medical conditions recorded in the eCRF who are sputum culture-negative 2 months after starting TB treatment by treatment group will be presented. Only subjects with sputum culture results prior to start of TB treatment and post-TB treatment performed in the same laboratory and on solid medium will be analysed for the main analysis. The similar summaries will be performed on all subjects with sputum results on solid medium regardless of laboratory in which they were collected. The similar summaries will be performed on the subset of subjects with liquid medium results regardless of laboratory in which they were collected. All data will be included in a listing.

11.4. Bayesian Analysis of Week 48 response rates

11.4.1. Brief Background

Given the small sample size of the current study, any frequentist estimation of response rates will be accompanied with high uncertainties. The aim of the analysis described in this section is to incorporate information from historical studies in the form of a prior distribution within a Bayesian analysis framework, in an attempt to increase precision of Week 48 response rate estimates. It is not anticipated that the precision estimated from the Bayesian analysis will be comparable to this from large studies where hundreds of patients are recruited, but important gains in statistical inference can be achieved by making the best use of historical trial information (Berry, 2006; Neuenschwander et al., 2010) which will aid with the overall interpretation of study results.

A fully Bayesian model which incorporates historical data in the form of dynamically down-weighted priors will be used for analysis (Schmidli et al., 2014). Two priors will be constructed: one for the response rate on the EFV arm and one for the treatment difference DTG ─ EFV (see more details in Appendix) which will then be combined to form a joint prior on the response rates of DTG and EFV. The response rate for the Bayesian analysis is defined as the proportion of subjects with HIV-1 RNA <50 copies/ml at Week 48 according to the Snapshot Algorithm.

11.4.2. Model Methodology

Let θ_{EFV} and θ_{DTG} be the probabilities of response at Week 48 in EFV and DTG arms, respectively. Let $D=\{Y_{EFV}, Y_{DTG}\}$ be the data observed in the current trial, that is the number of responders at Week 48 for EFV and DTG arms, respectively, and N_{EFV}, N_{DTG} be the total number of subjects in each arm. We denote with $f^R(\theta_{EFV}, \theta_{DTG})$ the joint prior of EFV and DTG response rates. The posterior distribution of response rates is given according to Bayes theorem by

$$f(\theta_{\text{EFV}}, \theta_{\text{DTG}}|D) = \frac{L(D|\theta_{\text{EFV}}, \theta_{DTG}) f^R(\theta_{EFV}, \theta_{DTG})}{f(D)} \quad (1)$$

where L is the likelihood and is given by

$$L(D|\theta_{EFV}, \theta_{DTG}) = \binom{Y_{\text{EFV}}}{N_{\text{EFV}}} \theta_{\text{EFV}}^{Y_{\text{EFV}}} (1-\theta_{\text{EFV}})^{N_{\text{EFV}}-Y_{\text{EFV}}} \binom{Y_{\text{DTG}}}{N_{\text{DTG}}} \theta_{\text{DTG}}^{Y_{\text{DTG}}} (1-\theta_{\text{DTG}})^{N_{\text{DTG}}-Y_{\text{DTG}}} \quad (2)$$

Assuming $Y_i \sim Binom(N_i, \theta_i), i = \text{DTG, EFV}$

and $f(D)$ is the marginal likelihood which is given by

$$f(D) = \int_0^1 \int_0^1 L(D|\theta_{\text{EFV}}, \theta_{DTG}) f^R(\theta_{\text{EFV}}, \theta_{DTG}) \mathrm{d}\theta_{\text{EFV}} \mathrm{d}\theta_{\text{DTG}} \quad (3)$$

11.4.3. Prior specification

We denote with $f^I_0(\theta_{\text{EFV}})$ an 'informative' prior on the EFV response rate constructed from a metanalysis of historical studies. This is the distribution Beta(291, 126) described in Appendix; so $f^I_0(\theta_{\text{EFV}})$ = Beta(θ_{EFV}; 291, 126).

We denote with $f^I_\Delta(\Delta|\theta_{\text{EFV}})$ an 'informative' prior on the treatment difference $\Delta = \theta_{\text{DTG}} - \theta_{\text{EFV}}$ constructed from a metanalysis of historical studies. This is a truncated version of the normal distribution described in Appendix; so $f^I_\Delta(\Delta|\theta_{\text{EFV}})$ = TN(Δ; 0.073, 0.023^2, $-\theta_{\text{EFV}}$, $1-\theta_{\text{EFV}}$). Truncation is needed because θ_{EFV} and θ_{DTG} take values in [0, 1].

We consider a robust version of these priors based on the robust mixture prior method of Schmidli et al., (2014) to downweight prior effect in posterior estimates in case of prior data conflict. The robustified version of these priors is given by

$$f^R_0(\theta_{\text{EFV}}) = w_{\text{EFV}} * f^I_0(\theta_{\text{EFV}}) + (1 - w_{\text{EFV}}) * f^U_0(\theta_{\text{EFV}}), \quad (4)$$

and

$$f^R_\Delta(\Delta|\theta_{\text{EFV}}) = w_{\text{Diff}} * f^I_\Delta(\Delta|\theta_{\text{EFV}}) + (1 - w_{\text{Diff}}) * f^U_\Delta(\Delta|\theta_{\text{EFV}}). \quad (5)$$

where $f^I_0(\theta_{\text{EFV}})$ and $f^I_\Delta(\Delta|\theta_{\text{EFV}})$ are described above, $f^U_0(\theta_{\text{EFV}})$ and $f^U_\Delta(\Delta|\theta_{\text{EFV}})$ are vague ('uninformative') priors and w_{EFV}, w_{Diff} are weights taking values in the range [0, 1]. In more detail $f^U_0(\theta_{\text{EFV}})$ = Beta(θ_{EFV}; 1, 1) and $f^U_\Delta(\Delta|\theta_{\text{EFV}})$ = TN(Δ; 0.073, 1^2, $-\theta_{\text{EFV}}$, $1-\theta_{\text{EFV}}$).

The bivariate robustified prior on θ_{EFV} and θ_{DTG} is then given by

$$f^R(\theta_{\text{EFV}}, \theta_{\text{DTG}}) = f^R_\Delta(\Delta|\theta_{\text{EFV}}) * f^R_0(\theta_{\text{EFV}}), \quad (6)$$

following the variable transformation $(\Delta, \theta_{\text{EFV}}) \rightarrow (\theta_{\text{DTG}}, \theta_{\text{EFV}})$: $\Delta = \theta_{\text{DTG}} - \theta_{\text{EFV}}$, $\theta_{\text{EFV}} = \theta_{\text{EFV}}$, on the joint prior $f^R(\Delta, \theta_{EFV}) = f^R_\Delta(\Delta|\theta_{\text{EFV}}) * f^R_0(\theta_{\text{EFV}})$ of (4) and (5).

11.4.4. Bayesian Analyses

Three Bayesian analyses will be conducted in total based on a selection of different choices of weights which correspond to three different priors. The weights, and thus the priors as specified in Section 11.4.3, for each analysis are shown below.

Analysis name	w_{EFV}	w_{Diff}	Comments
Main	0.6	0.7	
Sensitivity-1	0.9	0.9	'Optimistic' view of joint prior
Sensitivity-2	0.3	0.5	'Sceptical' view of joint prior

The first Bayesian analysis will be considered as the 'main' one while the other two are sensitivity analyses and are used to assess the impact of the choice of weights to posterior estimates in the main analysis. Sensitivity-1 analysis adopts an 'optimistic' view of the prior. Under the 'optimistic' scenario the informative prior components constructed from the historical studies are considered to be highly likely to reflect the truth based on clinical considerations and weights are then assigned according to results from Bayesian simulation. Sensitivity-2 analysis adopts a 'sceptical' view of the prior. Under the 'sceptical' scenario the informative prior components constructed from the historical studies are considered less likely to reflect the truth based on clinical considerations and weights are assigned accordingly taking into account simulation results. It is noted that in each of these views the same confidence or scepticism is given to both components of the prior; e.g. we don't put confidence on the prior EFV response rate but scepticism on the prior treatment difference or vice versa. These scenarios may be explored later as ad hoc analyses once results from the three analyses are available, if needed (e.g. in case discrepancies are observed in the posterior estimates among the three analyses).

A full description on the rational for the choice of weights for each analysis is described in the Appendix.

For the main Bayesian analysis the robustified bivariate prior on θ_{EFV} and θ_{DTG} is as follows:

$$f^R(\theta_{EFV}, \theta_{DTG}) = f^R_{\Delta}(\Delta|\theta_{EFV}) * f^R_0(\theta_{EFV}),$$

where

$$f^R_0(\theta_{EFV}) = 0.6 * \text{Beta}(\theta_{EFV}; 291, 126) + (1 - 0.6) * \text{Beta}(\theta_{EFV}; 1, 1)$$

and

$$f^R_{\Delta}(\Delta|\theta_{EFV}) = 0.7 * \text{TN}(\Delta; 0.073, 0.023^2, -\theta_{EFV}, 1 - \theta_{EFV}) + (1 - 0.7) * \text{TN}(\Delta; 0.073, 1^2, -\theta_{EFV}, 1 - \theta_{EFV})$$

The robustified bivariate priors for sensitivity analyses 1 and 2 are denoted in a similar way. All Bayesian analyses are considered exploratory.

Because the integral in the marginal likelihood (see eq. 3) is not analytically tractable MCMC will be used to calculate the joint posterior $f(\theta_{EFV}, \theta_{DTG} \mid D)$ as well as the marginal posteriors $f(\theta_{EFV}|D)$ and $f(\theta_{DTG}|D)$. SAS Proc MCMC and/or R/OpenBUGS will be used for analysis and QC.

Posterior inference of the EFV and DTG response rates will be based on the mean and 95% High Posterior Density (HPD) interval of the respective marginal posterior and results will be reported in a table. For each analysis, figures of joint and marginal posterior distributions will be constructed.

11.4.5. MCMC diagnostics

For each Bayesian analysis the following MCMC diagnostic checks should be performed.

- Trace plots for each variable to be constructed to check for convergence and autocorrelation.
- Tow chains of the MCMC algorithm should be used with different initial values. The posterior means and 95% HPDs from the two runs should be compared to check for convergence.
- The Gelman-Rubin convergence diagnostic should be used to check for convergence.

12. SAFETY ANALYSES

All safety displays will be based on the safety population, unless stated otherwise. Additional safety displays for all sites in Mexico for the study closeout will be summarized for serious and non-serious adverse events of Mexican subjects and serious adverse events for non-Mexican subjects. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables. Listings will present all available data, including from later phases which may not be summarized until future study reports. Listings will be grouped by the treatment groups of Table 3.

When descriptive statistics are used to summarize group characteristics or differences, the following statistics will be included: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

12.1. Extent of Exposure

The first and last doses and any changes/interruptions in dosing of investigator product will be listed for all subjects, together with details of the reason for any dose change/interruption. A repeat listing for Mexican subjects who had an adverse event will be provided separately at study closeout.

Distribution and summary statistics for the duration of exposure to IP (defined in Section 9.2.3) will be presented.

12.2. Adverse Events

Adverse events will be coded using the most recent MedDRA coding dictionary to give a preferred term and a system organ class. These preferred terms and system organ classes will be used when summarising the data. The verbatim text will be used in listings together with the preferred term. A listing of the relationship of preferred term to verbatim text will be presented ordered by system organ class.

The following summaries of Post-baseline AEs (i.e., those with Post-baseline onset date as defined in Section 9.2.13 and Section 9.3.1) will be tabulated:

1. All AEs by system organ class (SOC);
2. Common AEs by overall frequency;
3. All AEs by SOC and maximum toxicity;
4. Common Grade 2-4 AEs by overall frequency;
5. All drug-related AEs by SOC and maximum toxicity;
6. Common Grade 2-4 drug-related AEs by overall frequency;
7. Serious AEs (SAEs) by SOC;
8. Drug-related SAEs by SOC;
9. Fatal SAEs by overall frequency;
10. Drug-related Fatal SAEs by overall frequency;
11. AEs leading to withdrawal/permanent discontinuation of study treatment;
12. Proportion of subjects who temporarily discontinue IP due to AEs;
13. Proportion of subjects who temporarily discontinue TB therapy due to AEs;
14. Proportion of subjects who permanently discontinue TB therapy due to AEs/death;
15. Summary of Common Non-Serious Adverse Events by System Organ Class

Common AEs are those with ≥5% incidence for any treatment. For AEs reported more than once by a subject, the most severe intensity will be included in summaries where applicable.

Plots of incidence rates and relative risk for DTG vs. EFV for common AEs over 24/52 weeks of the Randomized Phase will be presented.

The following listings of AEs (including those occurring Pre-treatment and Post-treatment) will be provided:

1. All AEs;
2. Fatal SAEs;

3. Non-fatal SAEs;
4. AEs leading to permanent discontinuation of investigational product/withdrawal from the study;

Additionally, a listing of subject numbers for the individual adverse events will be presented for all Post-baseline AEs.

12.3. Deaths and Serious Adverse Events

Displays for deaths and SAEs that were reported during the study will be presented as detailed in Section 12.2. A listing of reasons for considering an AE as serious will be produced.

12.4. Adverse Events Leading to Discontinuation of Investigator Product Withdrawal from the Study and Other Significant Adverse Events

Adverse events leading to discontinuation of IP /withdrawal from the study will be reported as detailed in the Section 12.2.

12.5. TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS)

The proportion of subjects will be summarized by treatment group and maximum adverse event grade in the following:

- Proportion of subjects with no IRIS
- Proportion of subjects with no TB-Associated IRIS
- Proportion of subjects with adjudicated TB-associated IRIS
    - meet criteria for TB-associated IRIS
    - possibly meet criteria for TB-associated IRIS
- Proportion of subjects with suspected TB-associated IRIS but not possible to adjudicate

The results from EAC will be listed as well.

12.6. General (non-TB) Immune Reconstitution Inflammatory Syndrome (IRIS)

The proportion of subjects will be summarized by treatment group and maximum adverse event grade in the following:

- Proportion of subjects with no IRIS
- Proportion of subjects with no general IRIS
- Proportion of subjects with adjudicated general IRIS

  - meet criteria for general IRIS
  - possibly meet criteria for general IRIS
- Proportion of subjects with suspected general IRIS but not possible to adjudicate

The results from EAC will be listed as well.

12.7. Cardiovascular Events

A listing of subjects who experienced the cardiovascular events during the study will be provided. The cardiovascular events are listed below:

- 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

12.8. Suicidality Events

The number and percentage of subjects with a positive suicidal indication alert result by visit and treatment group will be summarized, excluding any false positive results. A positive suicidal indication alert is where there is level, 4 or 5 ideation, or any suicidal behaviour. Ideation levels 4 and 5 are where there is ideation but importantly there is intent to act on it. A false positive alert is one where the site determines the subject does not have suicidal risk, and/or there was an error recorded onsite. A listing of subjects who experience possible depression and/or suicidality-related adverse events along with the data from the Columbia-Suicide Severity Rating Scale (C-SSRS) will be listed. The C-SSRS suicidal ideation and behaviour data will also be listed, and a listing of false positive alerts with the investigator adjudication will also be provided.

12.9. Pregnancies

A listing of any subjects becoming pregnant during the study will be provided. The outcomes of any pregnancies will be described in the CSR, where available.

12.10. Clinical Laboratory Evaluations

The following laboratory evaluations will be collected at regular intervals throughout the trial:

- **Clinical chemistry:**
  - fasting lipids: triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL);
  - liver chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP);
  - electrolytes: sodium, phosphate, bicarbonate, chloride, potassium;
  - renal chemistries: blood urea nitrogen (BUN), creatinine, GFR (estimated by CKD-EPI);
  - other: creatine kinase (creatine phosphokinase [CPK]), lipase, glucose (fasted), albumin, PT/INR (screening visit only).
- **Hematology:**
  - platelet count, red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin, hematocrit, mean corpuscle volume (MCV);
  - WBC differential (count and %): neutrophils, lymphocytes, monocytes, eosinophils, basophils.
- **Other tests:**
  - Plasma HIV-1 RNA
  - CD4+ cell counts
  - Hepatitis B (HBsAg) and hepatitis C (anti-HCV Ab) (screening visit and Liver Stopping criteria follow-up evaluation only)
  - Pregnancy test for women of childbearing potential
  - HLA-B*5701 (screening visit only)

Data not provided in the GSK standard measurement units by the central laboratory will be converted by PPD using GSK's Integrated Data Standards Library (IDSL) standard conversions in the CONV dataset where necessary. Values for quantitative parameters provided as non-numeric, censored results from the central laboratory (e.g., '>100', '<1.9') will not be used when calculating summary statistics, but such values will be flagged (relative to normal ranges) and used where appropriate.

There was an issue with one of the Q2 instruments measuring creatinine concentrations between 1-Oct-2106 and 13-Jan-2017 and thus some creatinine values collected from this instrument at this period are unreliable. The affected creatinine samples collected from the defective instrument are described in a spreadsheet titled "ING117175 5BD.xlsx" (see also accompanied guidance document titled "Explanation of content in result spreadsheets Final.docx"). Values with "PASS" status were considered to be reliable after an evaluation the vendor performed based on a re-test of a refrigerated sample. If a re-test was not possible, "N/A" (Not Available) was recorded and the creatinine value is considered unreliable (see guidance document) and will be excluded from any analysis

and won't be reported in the outputs. The spreadsheet will serve as a guide to flag the unreliable values and exclude these values from any analysis.

12.10.1. Listings

Listings of laboratory data for subjects with abnormalities of potential clinical concern (i.e., Grade 1 or worse for chemistry/hematology) will be presented. These listings will contain normal range flags, fasting flags, and toxicity grades.

12.10.2. Summaries

12.10.2.1. Summary Statistics

Summary statistics for changes from baseline at each scheduled visit will be presented by treatment group. Separate summaries will be produced for each of chemistry and hematology; the summaries will include the baseline values (see Section 9.2.2). Creatinine, lipids, and glucose using mg/dL will also be summarized in addition to GSK standard units within the same table.

Summary statistics for the percentage change from baseline in lipids will be presented.

12.10.2.2. Toxicities

A toxicity is considered emergent if it develops or increases in intensity from baseline. The maximum Post-baseline emergent toxicity grade for each subject will be used within summaries.

The number and percentage of subjects with maximum Post-baseline emergent toxicities for each grade (Grade 1, Grade 2, etc.) will be summarized by parameter. Separate summaries will be produced for chemistry parameters and hematology parameters. Shift tables for creatinine will be produced, other parameters as necessary, showing baseline toxicity versus maximum Post-baseline toxicity.

A summary and listing of subjects meeting hepatobiliary laboratory abnormality criteria at any post-Baseline emergent visit will also be produced based on FDA Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009). In addition, a listing of all liver chemistry data for subjects meeting hepatobiliary laboratory abnormality criteria at any post-Baseline emergent visit will also be produced.

12.10.3. Figures

A scatter plot of maximum Post-baseline value versus baseline value will be presented for ALT. A scatter plot of maximum Post-baseline ALT values versus maximum Post-Baseline total bilirubin values will be presented. Such scatter plots may also be produced for other parameters or pairs of other parameters, as needed.

Liver chemistry profile plots will be produced for subjects meeting hepatobiliary lab abnormality criteria at any post-baseline emergent visit.

Other figures (such as line plots, box plots, etc.) of observed and changed from baseline values over time may be produced, as needed.

12.11. Other Safety Measures

12.11.1. Vital Signs

Vital signs data (blood pressure and heart rate) will be listed for each subject.

12.11.2. Suspected Abacavir Hypersensitivity Reaction (HSR)

Data recorded on the ABC HSR eCRF will be listed.

12.11.3. Liver Events

For subjects with liver chemistry results reaching or exceeding protocol-defined IP stopping criteria, the following data will be listed:

- liver event results exceeding the stopping criteria, and the time of the event relative to the start of IP and to the most recent IP;
- information on liver events that is used in the calculation of the RUCAM score;
- liver biopsy results;
- liver imaging results;
- past and current liver disease medical conditions;
- serology results from liver event follow-up (e.g., HCV RNA, hepatitis A IgM, CMV IgM antibody, etc.).

13. VIRAL GENOTYPING/PHENOTYPING

To assess the development of HIV-1 resistance in subjects who meet confirmed virologic withdrawal criteria over 24 and 48 weeks, the incidence of treatment-emergent genotypic and phenotypic resistance of HIV-1 PRO, RT and integrase to DTG, EFV, and other on-study ART in subjects meeting confirmed virologic withdrawal criteria will be listed using the ITT-E Population.

Listings will present all available data, including from later phases which may not be summarized until future study reports. Listings will be grouped by the treatment groups of Table 3.

13.1. Treatment-Emergent Genotype

For each drug class of mutations described in Section 8.5.1. A summary will be produced for treatment-emergent mutations for subjects with paired results (i.e., at both Day 1 and time of meeting virologic withdrawal criteria) for the applicable DNA region (i.e., integrase or PR/RT).

13.2. Treatment-Emergent Phenotype

The prevalence of treatment-emergent resistance to all ART will be summarized for the Viral Phenotypic population, once for resistance to each individual drug in each class, and again for resistance to numbers of drugs in each class.

14. PHARMACOGENETIC DATA ANALYSES

Refer to the protocol for information on pharmacogenetic analyses (Appendix 11.1).

15. PHARMACOKINETIC AND PHARMACOKINETIC/PHARMACODYNAMIC DATA ANALYSES

Week 24 interim analyses and Week 48 final analyses of DTG and EFV concentrations based on sparse PK sampling will be summarized by visit and sampling window using descriptive statistics. For any visit, subjects receiving DTG 50mg BID and DTG 50 mg QD should be summarized separately. PK samples with protocol deviations for DTG can be included for the purpose of summary statistics if samples are collected 1 hour prior to dose for pre-dose sample, within ±30 min window for 1-3hr post dose sample (i.e. between 0.5-3.5hr) and within ±60 min window for 4-12hr post dose sample (i.e. between 3-13hr). For subject with DTG twice daily dose, 4-12hr sample must be collected before second dose. For EFV any samples collected between 10-14hr will be included for summary statistics of mid-day plasma samples.

Concentrations of DTG and EFV at Weeks 8, 24, 36, and 48 upon initiation of DTG or EFV therapy will be analyzed using population PK modeling approach to estimate AUC, Cmax, and $C\tau$ for individual subjects at Week 48 final analysis. The relationship between DTG/EFV IP exposure and the Week 24 and Week 48 anti-HIV responses (Snapshot) may be evaluated using univariate (and multivariate) logistic regression analysis as well as graphic exploration. Details of the population PK and PK/PD analysis will be provided in a separate RAP and the population PK and PK/PD analysis results will be presented in a separate PK report.

16. REFERENCES

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17. ATTACHMENTS

17.1. Table of Contents for Data Display Specifications

17.1.1. Study Population

The ITT-E Population will be used, except where noted. The outputs are for both Week 24 and Week 48 reports, except where noted. All the completed outputs done at Week 24 only but for which the data has not changed will be delivered for all reports. For the closeout report, the tables, listings and figures below will be reviewed and selected as appropriate. The updated list will be provided in the appendix to the RAP revision.

17.1.1.1. Tables

Number	Title	Details/ Comments	Reports	IDSL/TST ID
6.1	Summary of Study Populations	All Subjects Screened Population		SA1
6.2	Summary of Screen Failures	All Subjects Screened Population	Week 24	ES6
6.3	Summary of Subjects by Country and Investigator		Week 24	
6.4	Summary of Subject Accountability: Randomized Phase Conclusion Record			ES1
6.5	Summary of Subject Accountability: OLE Phase Conclusion Record	ITT-OLE Population	Week 24 Week 48 Study Conclusion	ES1
6.6	Summary of Subject Accountability: Withdrawals from Study Treatment/Investigational Product by Visit			HIV_ES1
6.8	Summary of Important Protocol Deviations			DV1
6.9	Summary of Protocol Deviations Leading to Exclusion from the Per-Protocol Population			
6.10	Summary of Demographic Characteristics		Week 24	DM1
6.11	Summary of Age Ranges	EudraCT		DM11
6.12	Summary of Race and Racial Combinations		Week 24	DM5
6.13	Summary of Race and Racial Combinations Details		Week 24	DM6

Number	Title	Details/ Comments	Reports	IDSL/TST ID
6.14	Summary of Hepatitis Status at Entry		Week 24	
6.15	Summary of CDC Classification of HIV Infection at Baseline		Week 24	CDC1
6.16	Summary of Current Medical Conditions at Day 1		Week 24	MH1
6.17	Summary of Past Medical Conditions at Day 1		Week 24	MH1
6.18	Summary of Current Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		Week 24	MH4
6.19	Summary of Past Cardiac, Gastrointestinal, Metabolism and Nutrition, Psychiatric, Renal and Urinary, and Nervous System Conditions		Week 24	MH4
6.20	Summary of Current Tuberculosis (TB) Conditions at Screening		Week 24	
6.21	Summary of Cardiovascular Risk Assessments at Day 1		Week 24	
6.22	Distribution of Quantitative Plasma HIV-1 RNA (c/mL) Results at Screening and Baseline		Week 24	
6.23	Distribution of CD4+ Cell Count (cells/mm^3) Results at Screening and Baseline		Week 24	
6.24	Summary of Concomitant Medication by Ingredient ATC Level 1 – Randomized Phase			CM1
6.25	Summary of Concomitant Medication Ingredient Combinations - Randomized Phase			CM8
6.26	Summary of Concomitant Medication by Combination Term ATC Level 1 - Randomized Phase			CM1b
6.27	Summary of Prior Antiretroviral Therapy		Week 24	
6.28	Summary of Concomitant Antiretroviral Therapy - Randomized Phase			
6.29	Summary of TB Treatment Medications - Randomized Phase			
6.30	Summary of Subjects with Inclusion/Exclusion Criteria Deviations			

17.1.1.2. ICH Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
12.1	Listing of Screen Failures	All Subjects Screened Population	Week 24	ES7
12.2	Listing of Subjects Randomized But Not Treated	Randomized Population	Week 24	
12.3	Listing of Study Conclusion Record Reasons for Withdrawal			ES2
12.5	Listing of Subjects with Inclusion/Exclusion Criteria Deviations			IE3
12.6	Listing of Important Protocol Deviations			
12.7	Listing of Protocol Deviations Leading to Exclusion from the Per-Protocol Population			
12.8	Listing of Subjects Excluded from Any Population	ICH-E3		SP3
12.9	Listing of Demographic Characteristics		Week 24	DM2
12.10	Listing of Race		Week 24	DM9
12.11	Listing of Randomized and Actual Strata and Treatment Assignment	Randomized Population	Week 24	TA1

17.1.1.3. Other Listings

Number	Title	Details/Comments	Reports	IDSL/TST ID
13.1	Listing of Study Populations	All Subjects Screened Population	Week 24	
13.2	Listing of Subject Recruitment by Country and Site Number	All Subjects Screened Population	Week 24	
13.3	Listing of Visit Dates			
13.4	Listing of Hepatitis Test Results			
13.5	Listing of CDC Classification of HIV Infection at Baseline		Week 24	CDC3
13.6	Listing of Current and Past Medical Conditions		Week 24	MH2
13.7	Listing of Current and Past Medical Conditions for Mexican Subjects Who Had an Adverse Event		Study Closeout	MH2
13.8	Listing of Cardiovascular Risk Assessment Data at Day 1		Week 24	

Number	Title	Details/Comments	Reports	IDSL/TST ID
13.9	Listing of History of Cardiac Therapeutic Procedures		Week 24	
13.10	Listing of Investigational Product Accountability			
13.11	Listing of Prior, Concomitant, and Post-treatment Medications			CM2
13.12	Listing of Prior, Concomitant, and Post-treatment Medications for Mexican Subjects Who Had an Adverse Event		Study Closeout	CM2
13.13	Listing of Relationship Between ATC Level 1, Ingredient and Verbatim Text			CM6
13.14	Listing of Prior Antiretroviral Therapy		Week 24	CA3
13.15	Listing of Concomitant and Post-Treatment Antiretroviral Therapy			CA5
13.16	Listing of Concomitant Antiretroviral Therapy for Mexican Subjects Who Had an Adverse Event		Study Closeout	CA5
13.17	Listing of Relationship Between ATC Level 4, Combination, and Verbatim Text for ART			CA7
13.18	Listing of TB Treatment Medications			

17.1.2. Efficacy

The ITT-E Population will be used, except where noted. The outputs are for both Week 24 and Week 48 reports, except where noted. All the completed outputs done at Week 24 only but for which the data has not changed will be delivered for all reports. For the closeout report, the tables, listings and figures below will be reviewed and selected as appropriate. The updated list will be provided in the appendix to the RAP revision.

17.1.2.1. Tables

Number	Title	Details/ Comments	Reports	IDSL/TST ID
7.1	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis			
7.2	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis	Per-Protocol Population		
7.3	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 – Snapshot Analysis	MITT-E Population		
7.4	Summary of Study Outcomes (<50			

Number	Title	Details/ Comments	Reports	IDSL/TST ID
	c/mL) at Week 24/48 – Snapshot Analysis			
7.5	Summary of Study Outcomes (<50 c/mL) at Week 24/48 – Snapshot Analysis	Per-Protocol Population		
7.6	Summary of Study Outcomes (<50 c/mL) at Week 24/48 – Snapshot Analysis	MITT-E Population		
7.7	Summary of Proportion of Subjects with Plasma HIV-1 RNA < 50 c/mL by Visit – Snapshot Analysis			
7.8	Summary of Kaplan-Meier Estimates of Proportion of Subjects Neither Meeting Confirmed Virologic Withdrawal Criteria nor Discontinued due to Treatment Related Reasons Week 24/48			
7.9	Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit			
7.10	Distribution of Quantitative Plasma HIV-1 RNA Results at Time of Meeting Suspected and Confirmed of Virologic Withdrawal Criteria - Randomized Phase			
7.11	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24/48 by Subgroup - Snapshot Analysis			
7.12	Summary of CD4+ Cell Count (cells/mm^3) by Visit			
7.13	Summary of Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit			
7.14	Summary of Post-Baseline HIV-1 Associated Conditions Including Recurrences - Randomized Phase			
7.15	Summary of Post-Baseline HIV-1 Associated Conditions Excluding Recurrences - Randomized Phase			HIV1
7.16	Summary of Post-Baseline HIV-1 Disease Progressions - Randomized Phase			HIV1
7.17	Summary of Proportion of Subjects with TB Treatment Success - Randomized Phase		WK48	

Number	Title	Details/ Comments	Reports	IDSL/TST ID
7.18	Summary of TB Treatment Outcomes - Randomized Phase		WK48	
7.20	Summary of Proportion of Subjects with Sputum Culture Results on Solid Medium at 2 Months after Starting TB Treatment			
7.21	Summary of Proportion of Subjects with Sputum Culture Results on Liquid Medium at 2 Months after Starting TB Treatment			
7.22	Summary of Proportion of Subjects with Sputum Culture Results (Regardless of Medium) at 2 Months after Starting TB Treatment			
7.23	Summary of Proportion of Subjects with Sputum Smear Results at Month 2 after Starting TB Treatment			
7.24	Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit and Subgroup- Snapshot Analysis			TIGGER
7.25	Summary of Study Outcomes (<50 c/mL) at Week 24/48 by Subgroup - Snapshot Analysis			TIGGER
7.26	Bayesian Estimates of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL (Snapshot) at Week 48		WK48	

17.1.2.2. Figures

Number	Title	Details/ Comments	Reports	IDSL/TST ID
7.1	Proportion of Subjects with HIV-1 RNA <50 c/mL by Visit – Snapshot Analysis - Randomized Phase			
7.2	Kaplan-Meier Plot of Time to Meeting Virologic Withdrawal Criteria or Treatment Related Discontinuation - Randomized Phase			
7.3	Individual Plasma HIV-1 RNA Profiles by Visit - Randomized Phase			
7.4	Posterior Densities of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL (Snapshot) at Week 48		WK48	

17.1.2.3. ICH Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
12.21	Listing of Quantitative Plasma HIV-1 RNA Data			
12.22	Listing of Study Outcome (<50 c/mL) at Week 24/48 – Snapshot Analysis			

17.1.2.4. Other Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
13.21	Listing of CD4+ Cell Count Data			
13.22	Listing of HIV-1 Associated Conditions			HIV4
13.23	Listing of Sputum Assessment of TB Smear Results			
13.24	Listing of Tuberculosis and Susceptibility Culture Results			
13.25	Listing of TB Treatment Outcomes			
13.26	Listing of Subjects with Confirmed Virologic Withdrawal			
13.27	Listing of Tuberculosis and Susceptibility Culture and Nucleic Acid Amplification Results at Screening			

17.1.3. Safety

The Safety Population will be used, except where noted. The outputs are for both Week 24 and Week 48 reports, except where noted. All the completed outputs done at Week 24 only but for which the data has not changed will be delivered for all reports. For the closeout report, the tables, listings and figures below will be reviewed and selected as appropriate. The updated list will be provided in the appendix to the RAP revision.

17.1.3.1. Tables

Number	Title	Details/ Comments	Reports	IDSL/TST ID
8.1	Summary of Extent of Exposure to Investigational Product– Randomized Phase			
8.2	Summary of Extent of Exposure to Investigational Product – Randomization and OLE Phases		Week 24 Week 48 Study Closeout	
8.3	Summary of All Adverse Events by System Organ Class– Randomized			AE1

Number	Title	Details/ Comments	Reports	IDSL/TST ID
	Phase			
8.4	Summary of Common Adverse Events by Overall Frequency– Randomized Phase			AE3
8.5	Summary of All Adverse Events by System Organ Class and Maximum Toxicity– Randomized Phase			AE5
8.6	Summary of Common Grade 2-4 Adverse Events by Overall Frequency– Randomized Phase			AE3
8.7	Summary of All Drug-Related Adverse Events by System Organ Class and Maximum Toxicity – Randomized Phase			AE5
8.8	Summary of Common Drug-Related Grade 2-4 Adverse Events by Overall Frequency – Randomized Phase			AE3
8.9	Summary of Serious Adverse Events by System Organ Class – Randomized Phase			AE1
8.10	Summary of Drug-Related Serious Adverse Events by System Organ Class – Randomized Phase			AE1
8.11	Summary of Fatal Serious Adverse Events by Overall Frequency			AE3
8.12	Summary of Drug-Related Fatal Serious Adverse Events by Overall Frequency – Randomized Phase			AE3
8.13	Summary of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment – Randomized Phase			AE1
8.14	Summary of Common Non-Serious Adverse Events by System Organ Class – Randomized Phase			AE1 (modified)
8.15	Summary of Non-Serious Adverse Events by Preferred Term with Occurrences >=5%– Randomized Phase	FDAAA, EudraCT		AE15
8.16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurences) – Randomized Phase	FDAAA, EudraCT		AE16
8.17	Summary of Proportion of Subjects Temporarily Discontinued IP due to			

Number	Title	Details/ Comments	Reports	IDSL/TST ID
	Adverse Events– Randomized Phase			
8.18	Summary of Proportion of Subjects Temporarily Discontinued TB therapy due to Adverse Events– Randomized Phase			
8.19	Summary of Proportion of Subjects Permanently Discontinued TB Therapy due to Adverse Events/Death– Randomized Phase			
8.20	Proportion of Subjects with TB-Associated IRIS by Maximum Adverse Event Grade– Randomized Phase			
8.21	Proportion of Subjects with General (non-TB) IRIS by Maximum Adverse Event Grade– Randomized Phase			
8.22	Summary of Chemistry Changes from Baseline by Visit – Randomized Phase	Note: includes select parameters in conventional units (creatinine, lipids, glucose) and GFR derived by CKD-EPI and Total Cholestoral/HDL ratio.. Safety Population		LB1
8.23	Summary of Lipids Percentage Changes from Baseline by Visit– Randomized Phase			LB1
8.24	Summary of Hematology Changes From Baseline by Visit – Randomized Phase			LB1
8.25	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities– Randomized Phase	Include hyper/hypo (Table 9 in RAP)		
8.26	Summary of Maximum Post-Baseline Emergent Hematology Toxicities – Randomized Phase			
8.28	Summary of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria– Randomized Phase			

Number	Title	Details/ Comments	Reports	IDSL/TST ID
8.29	Summary of Positive Suicidal Indication Alerts Based on eCSSRS by Visit– Randomized Phase			
8.30	Summary of All Adverse Events by System Organ Class and Maximum Toxicity – Randomized and OLE Phases			AE5
8.31	Summary of All Drug-Related Adverse Events by System Organ Class and Maximum Toxicity – Randomized and OLE Phases			AE5
8.32	Summary of Serious Adverse Events by System Organ Class – Randomized and OLE Phass			
8.33	Summary of Drug-Related Serious Adverse Events by System Organ Class – Randomized and OLE Phases			
8.34	Summary of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment – Randomized and OLE Phases			
8.35	Summary of Lipids Percentage Changes from Baseline by Visit – Randomized and OLE Phases			
8.36	Summary of Maximum Post-Baseline Emergent Chemistry Toxicities – Randomized and OLE Phases			
8.37	Summary of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria – Randomized and OLE Phases			
8.38	Summary Cumulative Adverse Events – Randomized Phase			TIGGER
8.39	Summary of Subjects with C-SSRS Suicidal Ideation or Behaviour during Treatment			CSSRS1

17.1.3.2. Figures

Number	Title	Details/ Comments	Reports	IDSL/TST ID
8.1	Plot of Common Adverse Events and Relative Risk– Randomized Phase			AE10
8.2	Scatter Plot of Maximum Post-Baseline vs. Baseline for Alanine Aminotransferase (ALT) –			

Number	Title	Details/ Comments	Reports	IDSL/TST ID
	Randomized Phase			
8.3	Scatter Plot of Maximum Post-Baseline Alanine Aminotransferase (ALT) vs. Maximum Post-Baseline Total Bilirubin– Randomized Phase			
8.4	Liver Chemistry Profile Plots for Subjects Meeting Post-Baseline Emergent Hepatobiliary Lab Abnormality Criteria – Randomized Phase			LB11

17.1.3.3. ICH Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
12.31	Listing of Investigational Product Exposure Data			HIV_IP5
12.32	Listing of Investigational Product Exposure Data for Mexican Subjects Who Had an Adverse Event		Study Closeout	
12.33	Listing of All Adverse Events			AE8CP
12.34	Listing of Fatal Adverse Events			AE8CP
12.35	Listing of Non-Fatal Serious Adverse Events			AE8CP
12.36	Listing of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Investigational Product			AE8
12.37	Listing of Non-Serious Adverse Events of Mexican Subjects for Sites in Mexico		Study Closeout	
12.38	Listing of Serious Adverse Events of Mexican Subjects for Sites in Mexico		Study Closeout	
12.39	Listing of Serious Adverse Events of Non-Mexican Subjects		Study Closeout	
12.40	Listing of TB-Associated IRIS			
12.41	Listing of General IRIS			
12.42	Listing of Cardiovascular Events			
12.43	Listing of Subject Numbers for Individual Adverse Events			AE7

Number	Title	Details/ Comments	Reports	IDSL/TST ID
12.44	Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text			AE2
12.45	Listing of Clinical Chemistry Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern			
12.46	Listing of Hematology Laboratory Data for Subjects with Laboratory Abnormalities of Potential Clinical Concern			
12.47	Listing of Reasons for Considering as a Serious Adverse Event			
12.48	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1- Section 2)			PSRAE1
12.49	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)			PSRAE3
12.50	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)			PSRAE4
12.51	Listing of Possible Suicidality-Related Adverse Event Data (Section 5- Section 8)			PSRAE5
12.52	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL		MH2
12.53	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL		SU2
12.54	Listing of Post Baseline Maximum ALT and Maximum Bilirubin for subjects with ALT>=3xULN			

17.1.3.4. Other Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
13.31	Listing of Subjects Who Became Pregnant During the Study			PREG1a
13.32	Listing of Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Behavior Data			CSSRS4
13.33	Listing of Vital Signs			VS4
13.34	Listing of Abacavir Hypersensitivity Reaction Record - Exposure to Abacavir			ABC_HSR_EXPO2

Number	Title	Details/ Comments	Reports	IDSL/TST ID
13.35	Listing of Abacavir Hypersensitivity Reaction Record - Subject History of Drug Allergies			ABC_HSR_DRUG2
13.36	Listing of Abacavir Hypersensitivity Reaction Record - Subject and Family Conditions			ABC_HSR_COND2
13.37	Listing of Abacavir Hypersensitivity Reaction Record - Skin Rash Details			ABC_HSR_RASH2
13.38	Listing of Abacavir Hypersensitivity Reaction Record - Symptoms			ABC_HSR_SYMP4
13.39	Listing of Abacavir Hypersensitivity Reaction Record - Vital Signs			VS4
13.40	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Excluding Other Symptoms)			ABC_HSR_SYMP6
13.41	Listing of Abacavir Hypersensitivity Reaction Record - Individual Symptoms and Diagnostic Category Assignments (Other Symptoms)			ABC_HSR_SYMP7
13.42	Listing of Liver Monitoring/Stopping Event Reporting			LIVER5
13.43	Listing of Liver Event Information for RUCAM Score			LIVER6
13.44	Listing of Liver Biopsy Details			LIVER7
13.45	Listing of Liver Imaging Details			LIVER8
13.46	Listing of Past and Current Liver Disease Medical Conditions			MH2
13.47	Listing of Laboratory Data from Liver Event Follow-Up			LB5
13.48	Listing of Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria	same categories as Table 8.29		
13.49	Listing of All Liver Chemistry Data for Subjects Meeting Post-Baseline Emergent Hepatobiliary Laboratory Abnormality Criteria			LB5
13.50	Listing of False Positive Suicide Ideation			

17.1.4. Virology

17.1.4.1. Tables

Number	Title	Details/ Comments	Reports	IDSL/TST ID
9.1	Summary of IN Mutations for Subjects Meeting Confirmed Virologic Withdrawal Criteria– Randomized Phase	Viral Genotypic Population		
9.2	Summary of Treatment-Emergent IN Mutations for Subjects Meeting Confirmed Virologic Withdrawal Criteria– Randomized Phase	Viral Genotypic Population		
9.3	Summary of Genotypic Data of NRTI, NNRTI, and PI Classes for Subjects Meeting Confirmed Virologic Withdrawal Criteria – Randomized Phase	Viral Genotypic Population		
9.4	Summary of Treatment-associated Resistance Mutations – Confirmed Virological Withdrawal Subjects – Randomized Phase	Viral Genotypic Population		
9.5	Summary of Phenotype for Subjects Meeting Confirmed Virologic Withdrawal Criteria by Phenotypic Cut-off– Randomized Phase	Viral Phenotypic Population		
9.6	Summary of Phenotype for Subjects Meeting Confirmed Virologic Withdrawal Criteria: Number of Drugs to Which Subjects are Resistant– Randomized Phase	Viral Phenotypic Population		
9.7	Summary of Fold Change to DTG and to EFV at Baseline and at Time of Meeting Confirmed Virologic Withdrawal Criteria– Randomized Phase	Viral Phenotypic Population		

17.1.4.2. Other Listings

Number	Title	Details/Comments	Reports	IDSL/TST ID
13.51	Listing of Genotypic Data – Confirmed Virological Withdrawal Subjects	Viral Genotypic		
13.52	Listing of Treatment-associated Resistance Mutations – Confirmed Virological Withdrawal Subjects	Viral Genotypic		

Number	Title	Details/Comments	Reports	IDSL/TST ID
13.53	Listing of Phenotypic Data for Confirmed Virological Withdrawal Subjects	Viral Phenotypic population		
13.54	Listing of Replication Capacity	Viral Genotypic population		

17.1.5. PK

The PK Population will be used, except where noted.

17.1.5.1. Tables

Number	Title	Details/ Comments		Reports	IDSL/TST ID
10.1	Summary of Plasma DTG Concentrations by Visit – Once Daily				
10.2	Summary of Plasma DTG Concentrations by Visit – Twice Daily				
10.3	Summary of Plasma EFV Concentrations by Visit				

17.1.5.2. Figures

Number	Title	Details/ Comments	Reports	IDSL/TST ID
10.1	Plasma DTG Concentration Once Daily –Time Plot			
10.2	Plasma DTG Concentration Twice Daily –Time Plot			
10.3	Plasma EFV Concentration Once Daily –Time Plot			

17.1.5.3. Other Listings

Number	Title	Details/ Comments	Reports	IDSL/TST ID
13.61	Listing of DTG and EFV Plasma Concentrations			

17.2. Data Display Specifications

Data display specifications are available upon request.

17.3. Modified Snapshot Algorithm in Detail

Consider an arbitrary visit window, Week X. A subject's response (i.e., 'Virologic Success', 'Virologic Failure', or 'No Virologic Data at Week X') in that window is determined as follows, in the order stated:

5. If there was a non-permitted change in background ART (except a single protocol allowed switch in background ART) prior to Week X: Subject = Virologic Failure.
6. If non-permitted change in background ART during Week X

   AND:

   - no HIV-1 RNA result is available during Week X prior to change: Subject = Virologic Failure;
   - there is at least one HIV-1 RNA result available during Week X prior to the change, then consider the latest such result:

     i. if <50 c/mL: Subject = Virologic Success;

     ii. if ≥50 c/mL, Subject = Virologic Failure.
7. If there was no change or single protocol allowed switch in background ART prior or during Week X, then consider the latest On-Treatment HIV-1 RNA result during Week X:

   i. if <50 c/mL: Subject = Virologic Success;

   ii. if ≥50 c/mL: Subject = Virologic Failure.
8. If there is no change or single protocol allowed switch in background ART prior or during Week X and no HIV-1 RNA results are available during Week X:

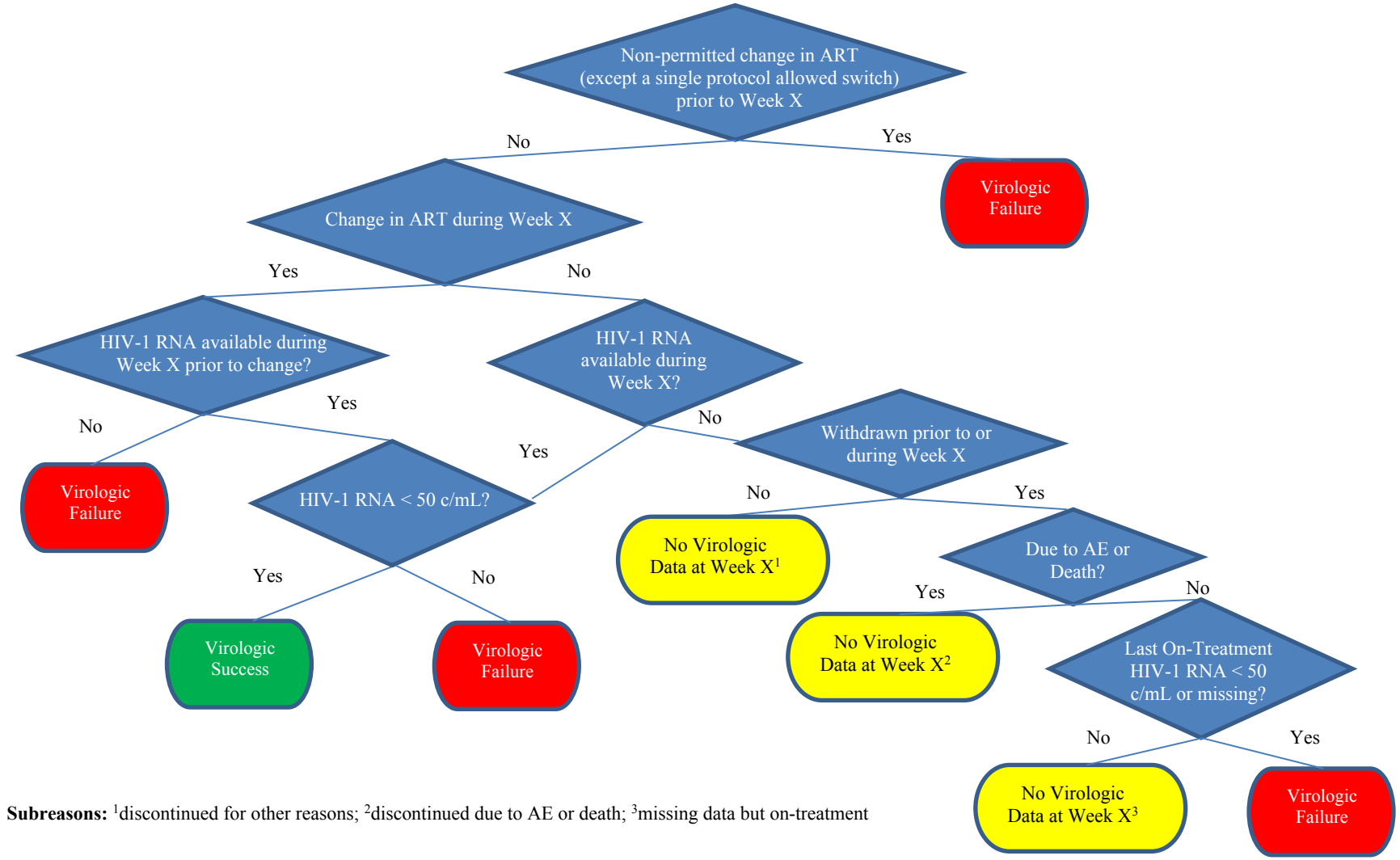
   - if the subject has not withdrawn from the study prior to or during Week X: Subject = No Virologic Data at Week X, with a reason of 'Missing data during window but on study';
   - if the subject was withdrawn from the study prior to or during Week X due to AE or death: Subject = No Virologic Data at Week X, with a reason of 'Discontinued due to AE or Death';
   - otherwise, consider the subject's last available On-treatment HIV-1 RNA result:

     iii. if <50 c/mL or no result is available: Subject = No Virologic Data at Week X, with a reason of 'Discontinued for Other Reasons';

     iv. if ≥50 c/mL: Subject = Virologic Failure.

To view a graphical representation of this algorithm, see Figure 4.

Figure 4 Modified Snapshot Algorithm



Subreasons: [1]discontinued for other reasons; [2]discontinued due to AE or death; [3]missing data but on-treatment

18. APPENDIX

18.1. Choosing weights for the informative components of joint prior Bayesian Simulation

Brief Background

The small sample size of the current trial does not allow a frequentist estimation of response rates (RR) with high precision. Incorporating information from historical studies within a Bayesian framework is likely to increase precision of RR estimates. This is expected to be the case particularly if data match the prior. In case of prior-data conflict, the use of prior information that is too optimistic (i.e. informative prior) may not be appropriate, as the posterior estimates can be driven mainly by the prior rather than by the data. The robust mixture prior method of Schmidli et al., (2014) is used to construct the final prior. This method incorporates a dynamic borrowing feature which enables the model to adapt the amount of borrowing (or down-weighting) of the historical information according to the degree of consistency between the historical and current data. This ensures that the potential for bias is controlled, and effectively allows the historical data to be ignored if the discrepancy between historical and current data is sufficiently large.

Two priors are constructed for the Bayesian historical studies analysis: one for the response rate on the EFV arm and one for the treatment difference DTG ─ EFV. No prior studies have examined the response rate at Week 48 in HIV/TB co-infected adults under a DTG containing regimen. Thus, the treatment difference from HIV-1 mono-infected population studies is used as there is no clinical evidence to support a different treatment difference in HIV/TB co-infected population (see more below in Clinical Considerations sections). By including prior information on the treatment difference in addition to that for EFV RR, we increase the overall prior information with a potential increase in precision of posterior estimates. The two priors are constructed independently, each from a metanalysis to combine response rate estimates from multiple relevant past studies. The two priors are then combined to construct a joint bivariate prior on the EFV and DTG response rates which is used for the Bayesian calculation of Week 48 response rate estimates of the current trial (more details on Section 11.4).

We collected information on EFV response rate in HIV/TB co-infected population from three historical studies and on DTG – EFV response rate difference in HIV-1 mono-infected population from two historical studies after a systematic bibliographic search. A metanalysis was performed to provide an overall estimate from the historical studies on EFV response rate and treatment difference (see below). Robustness of posterior estimates to prior information in case of prior data conflict can be achieved by adding a weakly-informative component to each of the informative components, i.e. for EFV and DTG – EFV constructed from the metanalysis of historical studies, as suggested by Schmidli et al., (2014). Thus the prior for the EFV response rate and the prior for the treatment difference become a mixture distribution of two components; an informative one constructed from the metanalysis of historical studies and a vague one which provides no preference to a particular value for the EFV response rate or treatment difference (e.g. a nearly flat distribution). The mixture of the two components (for each

of EFV and DTG – EFV) is constructed by assigning a weight to the informative component (the weight on the vague part of the mixture is 1 minus the weight on the informative part). The two mixtures (one for EFV and the other for DTG –EFV) are then combined and through a mathematical transform they form a joint prior for the EFV and DTG response rates to be used in the Bayesian analysis (see Section 11.4 for details).

Selection of Weights

The weight on the informative component of the EFV (w_{EFV}) and DTG – EFV (w_{Diff}) priors determine how quickly historical information is discounted in case of prior-data conflict. The weight w_{EFV} can be seen as the probability that the current trial matches the combined EFV response rate estimates of the historical studies. Similar interpretation can be given to w_{Diff}. Higher values reflect a stronger belief in the historical information and have a higher effect in the Bayesian estimates. A question arises on what the best selection of weights is in order to maintain the right balance between gains in precision in case of prior-data match, and loss of accuracy in case of prior-data conflict. A Bayesian simulation analysis was carried out to explore the operating characteristics for a combination of different values of weights under different assumptions for true EFV and DTG response rates. The rational for the final weights is described in the sections below and the choice of the weights has been based on two aspects: i) clinical considerations about the degree of confidence in the relevance of the historical data with the current study and ii) on the statistical simulation analysis to assess the precision and bias of posterior response rate estimates for given assumptions about the true treatment responses. From a statistical point of view, preferred weights are those which provide an appropriate balance between the potential gains in precision from including historical information that is consistent with the current study, versus the potential for increasing bias as the historical and current information diverges.

Details regarding the formulation of the joint prior, Bayesian simulation and metanalyses are provided elsewhere (see slide deck "Historical Studies Bayesian Simulation.pptx").

Metanalysis of Historical Studies

Historical studies on the EFV response rate

We conducted a systematic bibliographic search in PubMed to identify past studies which provide relevant historical information for the current study on the EFV response rate of an HIV/TB co-infected population at Week 48. We identified the following studies:

Study	EFV Response Rate
Bonnet et al., 2013	195/285 (68.4%)
Grinsztejn et al., 2014	37/51 (73%)
Manosuthi et al., 2016	52/71 (73.2%)

A Bayesian fixed-effects metanalysis was conducted to obtain an overall estimate of the response rate from the three studies (posterior mean: 0.70; 95% HPD: 0.65 - 0.74). The posterior distribution of the overall response rate estimate was approximated with a beta distribution, with the best-fit distribution to be Beta (291, 126).

Historical studies on the treatment difference DTG – EFV

We conducted a systematic bibliographic search in PubMed to identify past studies which provide relevant historical information for the current study on the difference (DTG – EFV) in response rates of DTG and EFV at Week 48 for the current study. We identified the following studies which refer to an HIV mono-infected population:

Study	DTG Response Rate	EFV Response Rate
Walmsley et al., 2013 (SINGLE)	364 / 414 (88%)	338 / 419 (81%)
Lunzen et al., 2012 (SPRING-1)	46 / 51 (90%)	41 / 50 (82%)

A Bayesian fixed-effects metanalysis was conducted to obtain an overall estimate of the treatment difference from the two studies (posterior mean: 0.073; 95% HPD: 0.028 - 0.119). The posterior distribution of the overall treatment difference was approximated with a normal distribution, with the best-fit distribution to be Normal(0.073, 0.023^2).

More information on the Bayesian metanalyses and approximation of posterior distributions is provided elsewhere (see slide deck "Historical Studies Bayesian Simulation.pptx").

Main Bayesian Analysis

Weights	
w_{EFV}	w_{Diff}
0.6	0.7

EFV

Clinical Considerations

1. The 3 independent studies, albeit small, gave relatively similar efficacy results: 68.4% to 73.2%
2. These studies are also highly relevant as they are in the HIV/TB co-infected population (as opposed to mono-infected were we saw 80% response rate for EFV in SINGLE and other mono-infected studies)
3. The limitation is that the population in the 3 studies from the prior include subjects with more advanced disease than the INSPIRING population (In Reflate, 27% of subjects had CD4 count <50 in the EFV arm, whereas in Inspiring subjects will have CD4 >50). Subjects with CD4 < 50 and with miliary or extrapulmonary TB (i.e. advanced TB) were included in these studies, and these subjects were excluded in INSPIRING). The inclusion of subjects with more advanced disease may increase the rates of adverse events/intolerance and study treatment discontinuations. Hence the EFV prior from the 3 studies may slightly underestimate the EFV RR that will be observed in INSPIRING.

4. Because of point 3 we are not completely confident that the RR in the historical information would match the EFV RR in INSPIRING, but since we do not expect the rates to be radically higher, a high weight (high confidence) seems reasonable.

Statistical Considerations

5. Bayesian simulation explored 9 scenarios regarding the true response rates for EFV and DTG, i.e. a combination of 0.60, 0.70 and 0.80 for EFV and 0.70, 0.80 and 0.85 for DTG. According to clinical judgement, 0.70 seems the most plausible scenario for EFV (which is in agreement with the prior). Simulation results suggest that under the assumption of a true EFV response rate of 0.70, no matter the assumption about the true DTG RR, the higher the weight for the EFV prior, the more accurate and precise is the Bayesian estimate of EFV response rate (see Figure 7E below for accuracy). Similarly, if the true EFV RR is somewhat higher as predicted by point 3, i.e., 0.70 – 0.75, then a high weight provides more accurate EFV RR estimates. If it is above 0.75, a smaller weight is preferable (see Figure 8B and Figure 8C).
6.
7. Because of points 1-5, the team decided on a wEFV=0.6. From a statistical perspective, if an EFV RR ≈ 0.70 is true, this will lead to a higher gain in accuracy (i.e. ~5% lower absolute relative error for 0.70 true EFV RR compared to a frequentist approach) compared to loss of accuracy if true EFV response rate is 0.6 or 0.8 (i.e. max ~3% higher absolute relative error compared to a frequentist approach; see Figure 7).

DTG – EFV

Clinical Considerations

1. The superior responses in the DTG arms in the historical studies were driven primarily by a lower rate of discontinuation due to adverse events/intolerance in the DTG–ABC–3TC group than in the EFV–TDF–FTC group. Differences in rates of discontinuation due to adverse events/intolerance between DTG and EFV is not expected to be any more or less in an HIV/TB co-infected population compared to an HIV- mono-infected population. Even though our study population is sicker and is subject to more polypharmacy, we can hypothesize that this impact would be equally applied to both arms. Hence, the treatment difference seen in mono-infected population is expected to be very similar for the HIV/TB co-infected population as well.
2. In INSPIRING, subjects receive EFV once daily, whereas DTG would need to be taken twice daily for as long the TB therapy is in place. The DTG BID dosing may impacting adherence, although this is not expected to be a big impact.

Statistical Considerations

3. Among the 9 scenarios explored the most plausible is the one with an EFV RR = 0.70 and a DTG RR = 0.80, which the joint prior closely matches. Under this scenario, simulation results favour a high weight for the treatment difference with the higher the weight the more accurate and precise is the Bayesian estimate of DTG response rate (see Figure 5E below and Figure 6B and Figure 6C for θ_{DTG}~0.80 regarding accuracy). If the true DTG RR is further away from 0.80, say <0.75 or >0.85 a smaller w_{Diff} will give less biased estimates (see Figure 6 for θ_{DTG}<0.75 & θ_{DTG}>0.80). How less biased the DTG RR estimate will be depends on the true value of EFV RR.

   From points 1-3 the team proposed a value of 0.7 for w_{Diff}.

Example

Table 15 shows what the Frequentist and Bayesian estimates will be if we observe Y_{EFV}=33 and Y_{DTG}=54 responders under this choice of weights. Y_{EFV} and Y_{DTG} were inferred assuming true θ_{EFV} = 0.74 and θ_{DTG} = 0.79 which sounds like a very likely scenario given the above clinical considerations.

Secondary Bayesian Analysis (Sensitivity Analyses)

A sensitivity analysis will be carried out adopting an 'optimistic' and 'sceptical' view of the joint prior.

Analysis Name	Weights		Comments
	w_{EFV}	w_{Diff}	
Sensitivity-1	0.9	0.9	'Optimistic' view of joint prior
Sensitivity-2	0.3	0.5	'Sceptical' view of joint prior

Optimistic view of prior: Sensitivity-1

Clinical Considerations

The 3 EFV historical studies are highly relevant for INSPIRING. The only limitation is that the INSPIRING population has less advanced disease population which can potentially lead to slightly higher EFV response rates. The prior from the 3 historical studies has a 95% CI of 0.65 – 0.74, so it covers values slightly higher than 0.70 which was the overall point estimate from the 3 historical studies. Under an optimistic view we should not expect much higher response rate values than 0.74 which are within the prior CI. For the treatment difference the clinical concern is that subjects receive DTG twice daily as long as they are under TB therapy and this could impact adherence (and potentially discontinuation) leading to lower DTG response rate and hence to a smaller treatment difference than in the historical studies. Yet, it is expected DTG subjects to

perform better (i.e. positive treatment difference). The 95% CI of the treatment difference prior is 0.03 – 0.12 and covers smaller treatment differences than 0.07. Under an optimistic view of the prior we don't expect treatment differences <0.03 but as low as 0.03 and upwards are plausible and are covered by the prior.

Statistical Considerations

From a statistical point of view, under the optimistic scenario that the joint prior reflects the true response rates, a choice of high w_{EFV} and w_{Diff} is recommended as they reduce bias in posterior estimates (see Figure 5E and Figure 7E for w_{Diff} and w_{EFV}, respectively) and increase precision. The team decided on the use of $w_{EFV} = 0.9$ and $w_{Diff} = 0.9$.

Example

Table 15 shows what the Frequentist and Bayesian estimates will be if we observe Y_{EFV}=32 and Y_{DTG}=52 responders under this choice of weights. Y_{EFV} and Y_{DTG} were inferred assuming true $\theta_{EFV} = 0.70$ and $\theta_{DTG} = 0.77$ which fully reflects the prior. Under an optimistic view, the prior matches perfectly the true rates.

Sceptical view of prior: Sensitivity-2

Clinical Considerations

Here we adopt a pessimistic view on the prior and we consider that it is rather unlikely to reflect the true response rates of EFV and DTG. If we assume that the prior on EFV is rather incorrect then based on the clinical argument about the "advanced disease population" a higher EFV RR than 0.70 is expected to be true. However, we expect this to be lower than ~0.82 which was the maximum observed response rate in the mono-infected population of SPRING-1 study. Under a pessimistic/sceptical view of the prior we expect true EFV RR to be >0.70 but probably not as high as 0.80, more likely something closer to 0.75, which is in the borders of the upper limit of the prior 95% CI (i.e. 0.74). Regarding the treatment difference, as noted above, the expectation is to be lower than 0.07 which was the historical point estimate. Under a sceptical view for the treatment difference we expect something closer to 0 but most likely not negative. So this sceptical view assumes true response rates ~0.75 for both EFV and DTG and this clinical thinking implies low weights to both w_{EFV} and w_{Diff}.

Statistical Considerations

Results from Bayesian simulation agree with a low w_{EFV}. If the true EFV RR is ~0.75 or slightly higher, a small w_{EFV} is preferable (e.g. see Figure 8B). So a choice of $w_{EFV} = 0.3$ seems reasonable and in line with clinical thinking.

Regarding the choice of w_{Diff}, at the extreme assumption of a true RR closer to 0.80 for both DTG and EFV, simulation results suggest in general a high value as this increases accuracy of the DTG response estimate (e.g. see Figure 5H). If true DTG RR is a bit lower, which is more plausible, again a high w_{Diff} is preferable (see Figure 6C for $0.75 \leq \theta_{DTG} < 0.80$). This is counterintuitive to what is implied from a clinical perspective. However, with a choice of $w_{EFV} = 0.3$, w_{Diff} has not too much impact (e.g. see bars for

w_{EFV}=0.3 in Figure 5H where the abs. rel. error ranges between 2.9% and 4.9% for different choices of w_{Diff} or compare within blue and red lines in Figure 6C for 0.75 ≤ θ_{DTG} < 0.80). The explanation why a high w_{Diff} is preferable from a stats point of view is as follows:

- The prior on EFV, even with a small w_{EFV}, has a mode on 0.70. Thus, a high w_{Diff} puts more confidence on a prior of 0.77 for the DTG response rate (given that the prior treatment difference is 0.07) which is very close to the assumption of true DTG RR of ~0.75. In contrast, a small w_{Diff} in this case provides no prior information on DTG RR and cannot correct for any inaccuracies observed in the data.

A value of w_{Diff}=0.5 might be a reasonable compromise between clinical and statistical perspective.

Example

Table 15 shows what the Frequentist and Bayesian estimates will be if we observe Y_{EFV}=34 and Y_{DTG}=51 responders under this choice of weights. Y_{EFV} and Y_{DTG} were inferred assuming true θ_{EFV} = 0.75 and θ_{DTG} = 0.75. Given that the withdrawal rate is 22% (at early May 2017) such a response rate is expected.

Examples

Table 15 Examples of Frequentist and Bayesian estimates of EFV and DTG response rates assuming different number of responders

Scenario	Y_{EFV}	Y_{DTG}	w_{EFV}	w_{Diff}	Frequentist $\hat{\theta}_{EFV}$ (95% CI)	Bayesian $\tilde{\theta}_{EFV}$ (95% CI)	Frequentist $\hat{\theta}_{DTG}$ (95% CI)	Bayesian $\tilde{\theta}_{DTG}$ (95% CI)
Main	33	54	0.6	0.7	0.73 (0.60, 0.86)	0.70 (0.66, 0.75)	0.79 (0.70, 0.89)	0.78 (0.72, 0.84)
Optimistic	32	52	0.9	0.9	0.71 (0.58, 0.84)	0.70 (0.66, 0.74)	0.76 (0.66, 0.87)	0.77 (0.71, 0.82)
Sceptical	34	51	0.3	0.5	0.76 (0.63, 0.88)	0.70 (0.64, 0.77)	0.75 (0.65, 0.85)	0.77 (0.69, 0.83)

Note: N_{EFV}=45, N_{DTG}=68

Figure 5 **Absolute Relative Error of Posterior DTG RR Estimate under different assumptions of true RR for EFV and DTG**

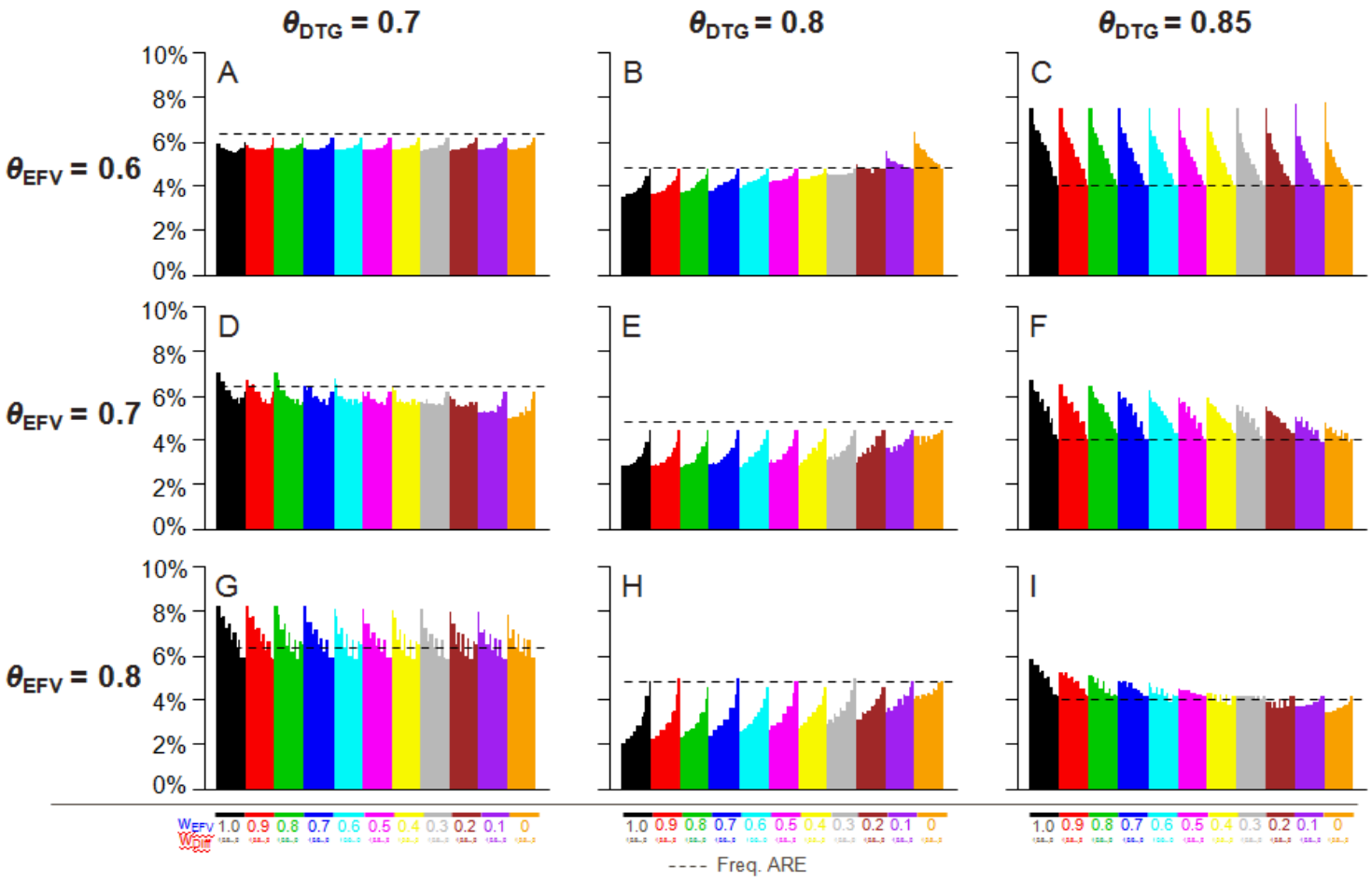


Figure 6 Absolute Relative Error of Posterior DTG RR Estimate under different assumptions of true RR for EFV and DTG

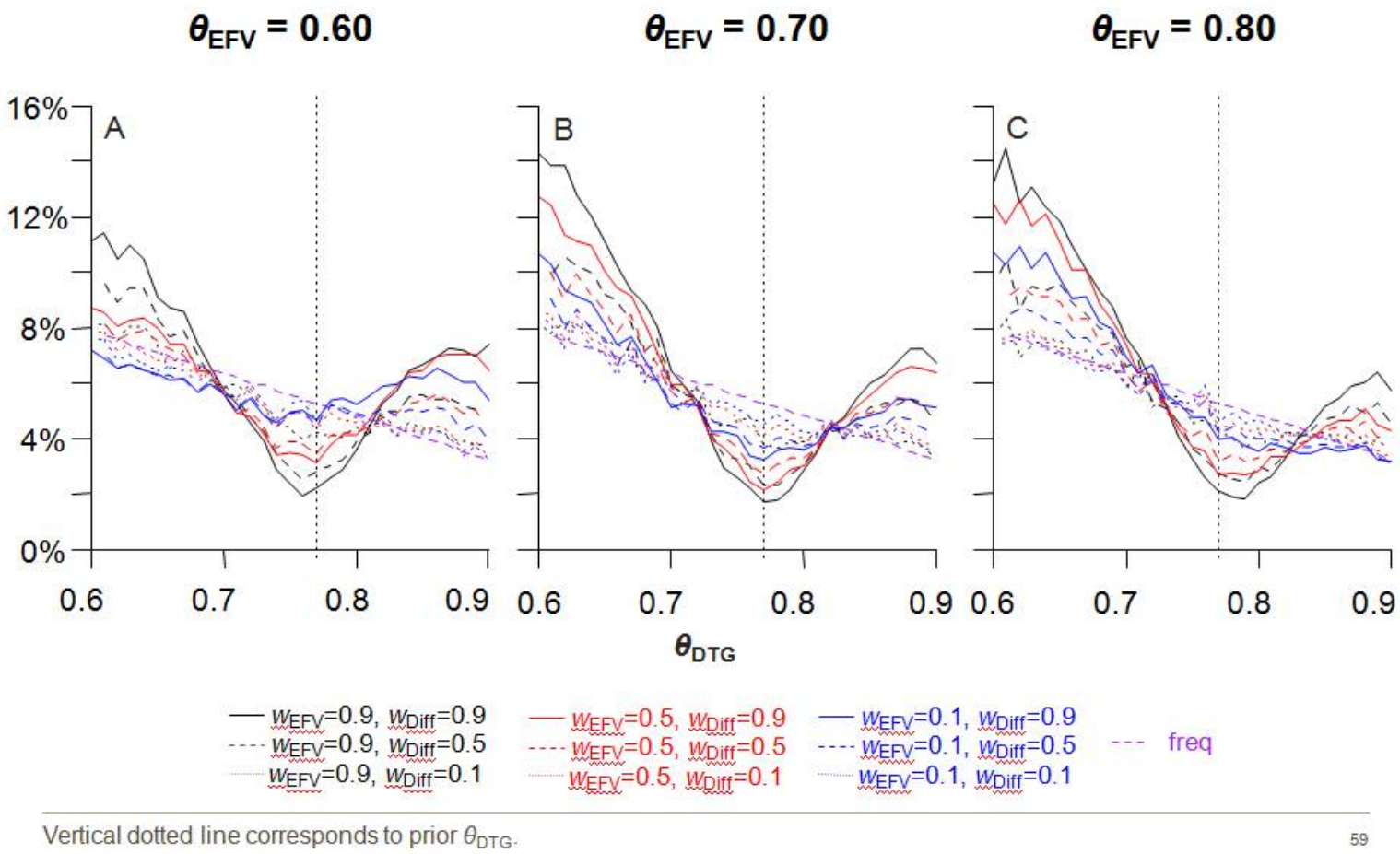


Figure 7 **Absolute Relative Error of Posterior EFV RR Estimate under different assumptions of true RR for EFV and DTG**

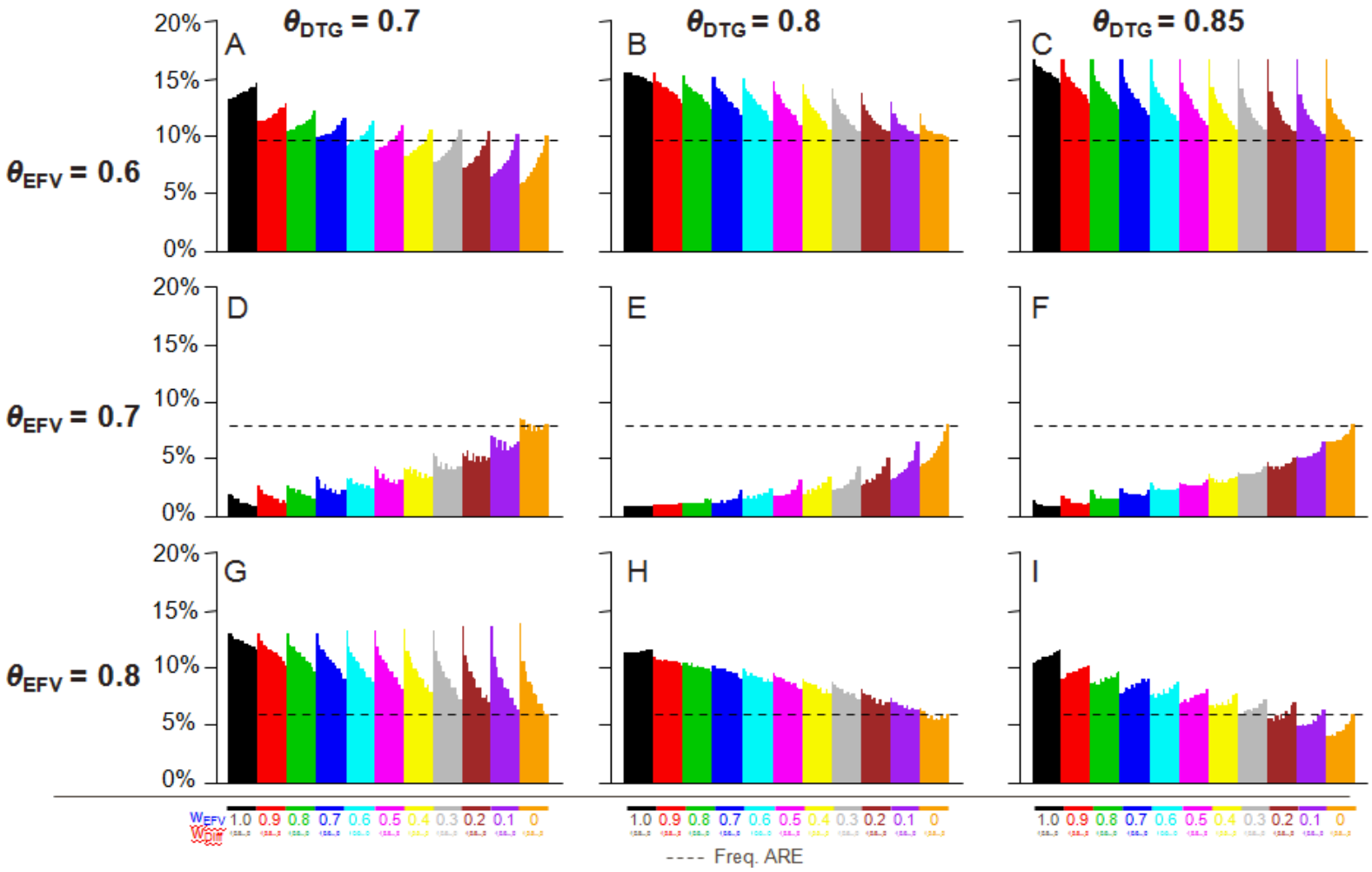


Figure 8 Absolute Relative Error of Posterior EFV RR Estimate under different assumptions of true RR for EFV and DTG