TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablet(s) of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine single entities and Food Effect Assessment in Healthy Volunteers

Compound Number: GSK3515864 (GSK1349572+GR109714)

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Author (s):

PPD

Clinical Statistics (PAREXEL)
Clinical Pharmacology Modelling & Simulation
Platform Technologies and Sciences
Infectious Diseases Medicines Discovery and Development
Research and Development, ViiV Healthcare
Clinical Pharmacology Science and Study Operations
Clinical Pharmacology Science and Study Operations

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N286215_00	2017-JAN-12	Original
2016N286215_01	2017-FEB-07	Amendment No. 1
Amendment 1 allows for an evaluation of a monolayer FDC tablet bioequivalence in Part 1 of the study and, if available, an evaluation of a bilayer FDC tablet bioequivalence in Part 2. The original protocol combined these bioequivalence evaluations into a single 3-way cross over design versus reference.		

SPONSOR SIGNATORY

PPD

2/7/17

Kimberly Y. Smith, MD
Vice President, Global PPD rategy
ViiV Healthcare Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

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Regulatory Agency Identifying Number(s): IND Number: 127475

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204994

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

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY 204994

Rationale

Treatment of human immunodeficiency virus (HIV) infection requires daily oral administration of a combination of at least three potent antiretroviral (ARV) drugs to reduce the patient's HIV levels. Lifelong adherence to these treatments is key to their success in decreasing HIV-related mortality and morbidity. Fixed dose combinations of these drugs have led to increase patient adherence and consequently reduce the likelihood of virological failure and viral resistance. However, since these regimens will need to be taken life-long, there is growing concern about their long-term toxicities and cost. Two-drug antiretroviral regimens may maintain virologic suppression while minimizing the adverse effects from cumulative drug exposure and reducing drug-related healthcare costs.

A combination of two potent, well-characterized and well-tolerated ARVs, dolutegravir (DTG, TIVICAY™), a HIV-1 integrase inhibitor (INI) and lamivudine (3TC; GR109714, EPIVIR™), a nucleoside analogue, may provide effective long-term antiviral suppression while limiting the risk of adverse reactions associated with ARV's. DTG and 3TC are indicated in combination with other antiretroviral agents for treatment in adults and children, and are each approved in the United States, European Union, and other countries for the treatment of HIV-1 infection. Two Phase 3 studies are ongoing to evaluate the safety and effectiveness of the co-administration of DTG and 3TC for the treatment of HIV-1 infection in antiretroviral-naive adult patients. Although the Phase 3 studies are being conducted with the individual entity products, the goal is to develop a fixed-dose combination (FDC) tablet of DTG and 3TC which can be taken once daily.

The purpose of the present study is to evaluate the bioequivalence of experimental FDC tablet(s) of DTG and 3TC relative to co-administration of the single entity products in healthy adult subjects. A monolayer FDC formulation was chosen based on the results from study 204993. In addition, a bilayer FDC tablet is being developed and will be included for Part 2, if available. This study will also assess the effect of food on these FDC formulation(s).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}.
Secondary	
• To characterize the PK profile of single dose FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state	• Plasma DTG and 3TC t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, Ct, and C_{24}
• To evaluate the food effect on FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg	• Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, Ct, and C_{24}.
• To assess the safety and tolerability from single-dose administration of the combination of DTG 50 mg, 3TC 300 mg in healthy volunteers either fasted or with a high fat meal.	• Safety and tolerability parameters as assessed by change from baseline vital signs (BP and HR), number of subjects with adverse events and toxicity grading of clinical laboratory tests

$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point
$AUC_{(0-\infty)}$ = area under the plasma concentration time curve from time zero to infinity
$AUC_{(0-24)}$ = area under the plasma concentration time curve from time zero to 24 hours
$\%AUC_{ex}$=% of $AUC_{(0-\infty)}$ that was extrapolated
C_{max} = maximum observed concentration
t_{max} = time of maximum observed concentration
C_{24} = concentration at 24h post-dose
Ct = last quantifiable concentration
PK = Pharmacokinetic
t = time of last quantifiable concentration
t_{lag} = absorption lag time
λz=apparent elimination rate constant
$t_{1/2}$ = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

Overall Design

This is a single-center, open-label, randomized, two-part study.

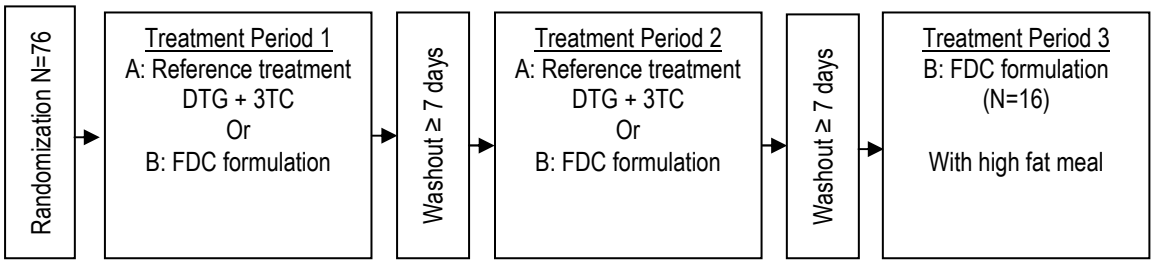
There will be a washout of at least 7 days between treatment periods and all subjects will return for a follow-up visit 7 to 14 days after the last dose of study drug. A 4-hour tolerance limit to the washout period will be permitted prior to dosing (i.e., -4 hours) to allow flexibility at the study site in scheduling subject return visits for subsequent periods 2 and 3.

<u>Part 1 – Bioequivalence and Food Effect with an FDC monolayer tablet</u>
Part 1 of the study will be a randomized, open-label, 2-period, single-dose, crossover study in 76 healthy adult subjects to achieve at least 70 evaluable subjects.

The first 16 subjects who complete the first two dosing periods, and consent to continue, will return for a third treatment period and receive a single dose of the FDC tablet formulation administered with a high fat meal.

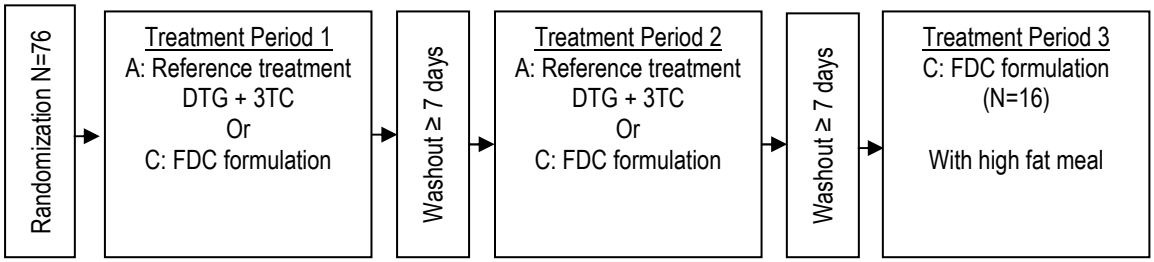
The purpose of Part 1 is to evaluate the bioequivalence (first two treatment periods) of oral DTG 50 mg/3TC 300 mg FDC tablet formulation (monolayer with Product Code AH) proposed for commercial use compared to co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and 3TC 300 mg (EPIVIR) and food effect (treatment period 3). For treatment periods 1 and 2, each treatment will be administered in the fasted state after at least 10 hours of fasting.

Figure 1 Study Design: Part 1, Bioequivalence and Food Effect with monolayer FDC tablet



Part 2 – Bioequivalence and Food Effect with an FDC bilayer tablet (Product Code TBD)
If another FDC formulation is available, Part 2 of the study will be conducted, similar to Part 1.

Figure 2 Study Design: Part 2, Bioequivalence and Food Effect with bilayer FDC tablet



Treatment Arms and Duration

Each subject will have a screening visit within 30 days prior to the first dose of study drug, three treatment periods each with a single dose of study drug and a follow-up visit within 7-14 days after the last dose of study drug. There will be a washout of at least 7 days (-4 hours) between each dose of study drug. The total duration of participation of a subject in this study will be approximately 11 weeks.

Type and Number of Subjects

A minimum of 76 healthy adult subjects will be randomized such that a minimum of approximately 70 evaluable subjects complete treatment periods 1 and 2 of Part 1 of the study. A total of 16 subjects, who complete treatment periods 1 and 2 and provide consent will continue and participate in period 3 of the study, in Part 1.

If Part 2 of the study is conducted, another 76 healthy adult subjects will be randomized such that a minimum of approximately 70 evaluable subjects complete treatment periods 1 and 2 of Part 2 of the study. A total of 16 subjects who complete treatment periods 1 and 2 and provide consent will continue and participate in period 3 of the study, in Part 2.

Analysis

Interim Analysis

Following completion of Part 1, preliminary PK data from Part 1 will be analyzed. The point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment (monolayer) to the geometric mean of the reference treatments, μ(test)/μ(reference) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} for both DTG and 3TC. The result will be used for planning a future Phase III study.

An independent statistical and programming team will perform the preliminary PK analysis. As the PK data are analysed separately for each part of the study, there will be no adjustments for multiplicity.

Final Analysis

Final analyses will be performed after the completion of the study and final database authorization.

Primary and Secondary Analyses

PK analyses will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK or their designee. Plasma DTG and 3TC concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, $t_{1/2}$, t_{lag}, C_t, C_{24}, λz, $\%AUC_{ex}$, Vz/F, t and CL/F.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline or their designee.

The PK parameters for DTG and 3TC (except t_{max} and t_{lag}) will be log_e-transformed and separately analyzed using a mixed effects model. For the analysis of bioequivalence, the model will include fixed effect terms for period and treatment. Subject will be treated as a random effect in the model. For the analysis of food effect, the model will include a fixed effect term for treatment (fed versus fasted) and a random effect term for subject.

Point estimates and their associated 90% confidence intervals (CIs) will be constructed for the differences in PK parameter values between test and reference treatments for the treatment comparisons. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of PK parameters between test and reference treatments.

T_{max} and T_{lag} of DTG and 3TC will be separately analyzed with the non-parametric Wilcoxon matched pair method to compute point estimates and associated 90% confidence intervals for the median differences between test and reference treatments.

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

2. INTRODUCTION

2.1. Study Rationale

Treatment of human immunodeficiency virus (HIV) infection requires daily oral administration of a combination of at least three potent antiretroviral (ARV) drugs to reduce the patient's HIV levels. Lifelong adherence to these treatments is key to their success in decreasing HIV-related mortality and morbidity. Fixed dose combinations of these drugs have led to increase patient adherence and consequently reduce the likelihood of virological failure and viral resistance. However, since these regimens will need to be taken life-long, there is growing concern about their long-term toxicities and cost. Two-drug antiretroviral regimens may maintain virologic suppression while minimizing the adverse effects from cumulative drug exposure and reducing drug-related healthcare costs.

A combination of two potent, well-characterized and well-tolerated ARVs, dolutegravir (DTG, TIVICAY™), a HIV-1 integrase inhibitor (INI) and lamivudine (3TC; GR109714, EPIVIR™), a nucleoside analogue, may provide effective long-term antiviral suppression while limiting the risk of adverse reactions associated with ARV's. DTG and 3TC are indicated in combination with other antiretroviral agents for treatment in adults and children, and are each approved in the United States, European Union, and other countries for the treatment of HIV-1 infection. Two Phase 3 studies are ongoing to evaluate the safety and effectiveness of the co-administration of DTG and 3TC for the treatment of HIV-1 infection in antiretroviral-naive adult patients. Although the Phase 3 studies are being conducted with the individual entity products, the goal is to develop a fixed-dose combination (FDC) tablet of DTG and 3TC which can be taken once daily.

The purpose of the present study is to evaluate the bioequivalence of experimental FDC tablet(s) of DTG and 3TC relative to co-administration of the single entity products in healthy adult subjects. The monolayer FDC formulation was chosen based on the results from study 204993 (GlaxoSmithKline Document Number 2015N258080_00. In addition, a bilayer FDC tablet is being developed and will be included, if available. This study will also assess the effect of food on the FDC formulation(s).

2.2. Brief Background

DTG is an HIV-1 integrase inhibitor with low to moderate inter-subject pharmacokinetic (PK) variability, a predictable exposure-response relationship, and a 14 hour plasma half-life. Although co-administration of DTG with low-, moderate-, and high-fat meals in Study ING113674 (GlaxoSmithKline Document Number 2010N105142_00) increased DTG exposures (area under the plasma concentration-time curve from time 0 to infinity $AUC_{(0-\infty)}$) by 33%, 41%, and 66%, respectively, the TIVICAY product label states that the approved dose regimen is 50 mg once daily taken with or without food based on efficacy and safety results of Phase 3 trials where DTG was taken without regard to mealtimes. DTG is available as the single entity product TIVICAY and as a component of the FDC product TRIUMEQ (DTG/abacavir (ABC)/lamivudine (3TC). Bioequivalence was demonstrated between DTG/ABC/3TC (TRIUMEQ) and the separate co-administered tablet formulations of TIVICAY plus ABC/3TC FDC

(EPZICOM) in the pivotal bioequivalence and food effect study for TRIUMEQ in Study ING114580 (GlaxoSmithKline Document Number 2012N145882_00). The effect of food on DTG when administered as DTG/ABC/3TC FDC (TRIUMEQ) in study ING114580 was similar to the effect of food on a 50 mg DTG (ING113674) dose and was not considered clinically significant. More information on the efficacy, PK, safety and drug interaction potential of DTG based on an extensive program of Phase I to III clinical trials can be found in the Investigator Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/07]).

Lamivudine (3TC) is an approved synthetic nucleoside reverse transcriptase inhibitor (NRTI) with activity against HIV and hepatitis B (HBV). Intracellularly, 3TC is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is the inhibition of HIV-1 reverse transcriptase via deoxyribonucleic acid (DNA) chain termination after incorporation of the nucleoside analogue into viral DNA. 3TC is well absorbed from the gastrointestinal tract with an absolute oral bioavailability in adults of 86% to 88% for liquid and solid dosage forms with Time to observed maximal drug concentration (T_{max})of approximately 1 hour. 3TC may be administered with or without food. 3TC exhibits dose-proportional PK at steady state following repeat doses of 0.25 to 10 mg/kg twice daily. 3TC is available as the single entity product EPIVIR and as a component of the following FDC products: COMBIVIR (zidovudine/3TC), EPZICOM/KIVEXA (ABC/3TC), TRIZIVIR (ABC/3TC/zidovudine), TRIUMEQ (DTG/ABC/3TC).

No significant food effect was observed for 3TC when administered as 3TC alone (study NUCA1001), as DTG/ABC/3TC (TRIUMEQ) in study ING114580, or as ABC/3TC FDC (EPZICOM) in study CAL10001 (GlaxoSmithKline Document Number RM2002/00116/00).

In a relative bioavailability study conducted in the fasted state, 204993, two experimental monolayer FDC tablet formulations of DTG/3TC were evaluated and compared to co-administration of the separate formulations of DTG 50 mg clinical image and a single EPIVIR™ 300 mg tablet, in healthy volunteers 18 to 65 years of age. All formulations of DTG/ 3TC were well-tolerated in this study. No deaths, serious adverse events (SAEs), or adverse events (AEs) leading to withdrawal from the study occurred. No clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed during the study. The results for the primary endpoints of this study showed are shown in Table 1.

Table 1 Statistical Comparisons of DTG and 3TC AUC(0-∞) and Cmax Following Administration of two FDC Tablets (Product Code AA and AB) versus Reference (Co-administration of the Separate Formulations of DTG 50 mg Clinical Image and a Single EPIVIR™ 300 mg)

PK Parameters	DTG		3TC	
	Ratio of Geometric Least Squares Means (90% Confidence Interval)			
	Product Code AA (n=29) vs. Reference (n=30)	Product Code AB (n=29) vs. Reference (n=30)	Product Code AA (*n=29) vs. Reference (*n=30)	Product Code AB (*n=29) vs. Reference (*n=30)
$AUC_{(0-\infty)}$ (h.ug/mL)	1.122 (1.005, 1.252)	1.015 (0.909, 1.132)	1.033 (0.991, 1.078)	1.030 (0.988, 1.074)
C_{max} (μg/mL)	1.145 (1.025, 1.278)	1.020 (0.913, 1.140)	1.178 (1.080, 1.284)	1.231 (1.129, 1.342)

DTG=Dolutegravir; 3TC=Lamivudine; AUC(0-∞)=AUC from time 0 extrapolated to infinity; Cmax=maximum observed concentrations;
*For 3TC, $\underline{AUC}_{(0-\infty)}$: n=28 for reference, n=26 for product code AA, n=27 for product code AB. $\underline{AUC}_{(0-\infty)}$ for 5 subjects was excluded because the duration for the calculation of λ_z (apparent terminal slope) was <2x the calculated λ_z and/or the R squared adjusted was < 0.85.

In brief, for the monolayer FDC tablet code AA, the DTG C_{max} and $AUC_{(0-\infty)}$ were approximately 14.5% and 12.2% higher than those following the reference treatment (DTG 50 mg tablet (clinical image) plus EPIVIR 300 mg tablet). The 3TC $AUC_{(0-\infty)}$ was similar to the reference treatment however, the 3TC C_{max} was 17.8% higher than that for the reference treatment. For the monolayer FDC tablet code AB, the DTG C_{max} and $AUC_{(0-\infty)}$, and the 3TC $AUC_{(0-\infty)}$ were similar to those from the reference; however, the 3TC C_{max} was 23.1% higher than that from the reference.

The DTG/3TC FDC monolayer tablets used in study 204993 are similar in formulation with the approved TRIUMEQ formulation, minus the ABC component, which was shown to be bioequivalent to the separate co-administered tablet formulations of TIVICAY plus ABC/3TC FDC (EPZICOM) in Study ING114580. A comprehensive analysis of the study conduct, inclusion/exclusion criteria, dissolution characteristics and impact of the demographic characteristics on the PK profiles and variability was unable to provide a clear explanation of the observed differences between the test and reference formulations.

In study 204993, product codes AA and AB contained the same quantitative composition and varied in the processing conditions used to manufacture the DTG granule. The proposed study will use product code AH which has the same quantitative composition with the dolutegravir granule manufactured at the 300L commercial scale, which results in an *in vitro* dissolution profile for dolutegravir that falls between what was observed for product codes AA and AB in study 204993.

In addition, to the monolayer tablet FDC (product code AH), a bilayer FDC tablet is being developed. The monolayer formulation is the preferred formulation for commercial development due to the lower complexity of manufacturing.

A flexible study design is proposed due to the uncertainty of whether or not a robust formulation for the bilayer tablet can be developed. Part 2 of the study, incorporating the bilayer FDC formulation, will only be conducted if a suitable formulation is available.

Part 1:

Treatment periods 1 and 2 are a single-dose, crossover pivotal bioequivalence evaluation of the DTG/3TC FDC monolayer formulation tablet. The reference formulation will be the 50 mg DTG clinical image and 3TC 300 mg tablet (EPIVIR).

Period 3 will evaluate the effect of a high fat meal on the FDC monolayer tablet formulation. As an increase in exposure has been previously shown when DTG was co-administered with a high fat meal (ING113674), this portion of the study is not powered to demonstrate bioequivalence. These data will be used to assess whether a similar food effect is observed with the FDC tablet as is seen with the single DTG entity. A high fat meal was selected as this has shown the largest increase in DTG exposure compared with low- and moderate- fat meals.

Part 2:

Treatment periods 1 and 2 will be conducted with the identical design as in Part 1, and evaluate the bioequivalence of a bilayer DTG/3TC FDC formulation tablet. The single entity reference formulations mentioned above will also be used in Part 2 (treatment periods 1 and 2). The food effect of the bilayer FDC tablet will be evaluated in Period 3 of Part 2.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}.
Secondary	
• To characterize the PK profile of single dose of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state	• Plasma DTG and 3TC t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, Ct, and C_{24}
• To evaluate the food effect on FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg	• Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, Ct, and C_{24}.
• To assess the safety and tolerability from single-dose administration of the combination of DTG 50 mg, 3TC 300 mg in healthy volunteers either fasted or with a high fat meal.	• Safety and tolerability parameters as assessed by change from baseline in vital signs (BP and HR), number of subjects with adverse events and toxicity grading of clinical laboratory tests

$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point
$AUC_{(0-\infty)}$ = area under the plasma concentration time curve from time zero to infinity
$AUC_{(0-24)}$ = area under the plasma concentration time curve from time zero to 24 hours
$\%AUC_{ex}$=% of $AUC_{(0-\infty)}$ that was extrapolated
C_{max} = maximum observed concentration
t_{max} = time of maximum observed concentration
C_{24} = concentration at 24h post-dose
Ct = last quantifiable concentration
PK = Pharmacokinetic
t = time of last quantifiable concentration
t_{lag} = absorption lag time
λz=apparent elimination rate constant
$t_{1/2}$ = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

4. STUDY DESIGN

4.1. Overall Design

This is a single-center, open-label, randomized, two-part study.

There will be a washout of at least 7 days between treatment periods and all subjects will return for a follow-up visit 7 to 14 days after the last dose of study drug. A 4-hour tolerance limit to the washout period will be permitted prior to dosing (i.e., -4 hours) to allow flexibility at the study site in scheduling subject return visits for subsequent periods 2 and 3.

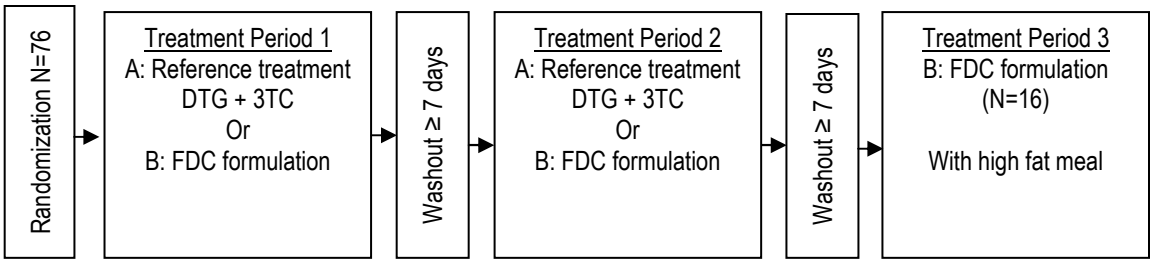
Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct.

4.1.1. Part 1: Bioequivalence and Food Effect with a FDC monolayer tablet

Part 1 of the study will be a randomized, open-label, 2-period, single-dose, crossover study in 76 healthy adult subjects to achieve at least 70 evaluable subjects. The first 16 subjects who complete the first two dosing periods, and consent to continue, will return for a third treatment period and receive a single dose of the FDC tablet formulation administered with a high fat meal.

The purpose of Part 1 is to evaluate the bioequivalence (first two treatment periods) of oral DTG 50 mg/3TC 300 mg FDC tablet formulation (monolayer with Product Code AH) proposed for commercial use compared to co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and 3TC 300 mg (EPIVIR) and food effect (treatment period 3). For treatment periods 1 and 2, each treatment will be administered in the fasted state after at least 10 hours of fasting.

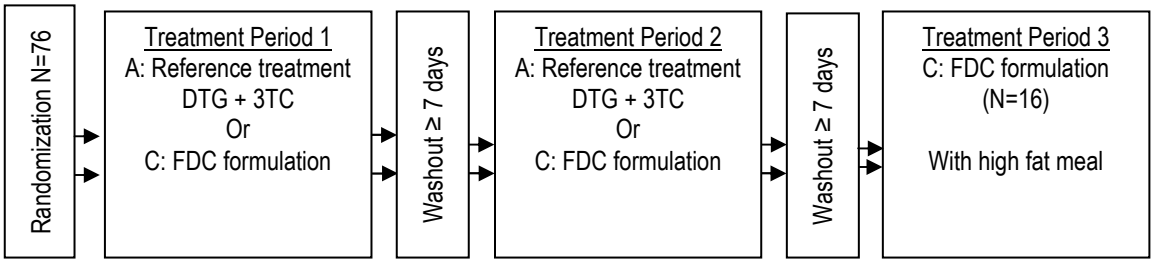
Figure 3 Study Design: Part 1, Bioequivalence and Food Effect with monolayer FDC tablet



4.1.2. Part 2 – Bioequivalence and Food Effect with an FDC bilayer tablet

Part 2 of the study, incorporating the bilayer FDC formulation, will only be conducted if a suitable formulation is available.

Figure 4 Study Design – Part 2, Bioequivalence and Food Effect with bilayer FDC formulation (if conducted)



4.2. Treatment Arms and Duration

Each subject will have a screening visit within 30 days prior to the first dose of study drug, up to three treatment periods each with a single dose of study drug and a follow-up visit within 7-14 days after the last dose of study drug. There will be a washout of at least 7 days (-4 hours) between each dose of study drug. The total duration of participation of a subject in this study will be approximately 11 weeks.

4.3. Type and Number of Subjects

A minimum of 76 healthy adult subjects will be randomized such that a minimum of approximately 70 evaluable subjects complete treatment periods 1 and 2 of Part 1 of the study. A total of 16 subjects who complete treatment periods 1 and 2 and provide consent will continue and participate in period 3 of the study, in Part 1.

If Part 2 of the study is conducted, another 76 healthy adult subjects will be randomized such that a minimum of approximately 70 evaluable subjects complete treatment periods 1 and 2 of Part 2 of the study. A total of 16 subjects who complete treatment periods 1 and 2 and provide consent will continue and participate in period 3 of the study, in Part 2.

Evaluable subjects are defined as all subjects who provide sufficient concentration-time profiles to calculate valid PK parameters for both analytes for Period 1 and Period 2 without important protocol violation. Data from subjects who vomit within 4 hours of study drug administration will not be considered as evaluable.

If subjects prematurely discontinue the study for reasons other than adverse event (AE), additional replacement subjects may be randomized and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

4.4. Design Justification

This primary objective of this study is to evaluate the bioequivalence of DTG and 3TC when administered as a FDC tablet compared to the co-administration of the 2 single

entity products in the fasted state. Two FDC formulations will be tested (a monolayer [preferred formulation] and a bilayer formulation, if available). In addition, an evaluation of the effect of food on the FDC formulation(s) will be conducted.

A cross-over design was selected for this study so that within subject comparisons can be utilized to reduce the number of subjects required for the study. The half-life of DTG and 3TC requires at least a 7-day washout between DTG and 3TC doses and a 72-hour PK sampling period to ensure that pre-dose concentrations are negligible and that PK parameters are well-estimated.

4.5. Dose Justification

The United States Food and Drug Administration (US FDA)-approved adult dose of DTG for treatment-naive and non-INI resistant treatment-experienced HIV-infected patients is 50 mg once daily, in combination with other antiretroviral drugs.

The US FDA-approved recommended adult dose of 3TC for treatment naive HIV-infected patients is 300 mg once daily, in combination with other antiretroviral drugs.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG or DTG in combination with 3TC can be found in the Investigator's Brochure (GlaxoSmithKline Document Number RM2007/00683/07) and product labels for DTG and 3TC. The following section outlines the risk assessment and mitigation strategy for this protocol. Of note, the events noted in the table below were observed with the repeated doses of DTG and 3TC. The risk of these events would be significantly lower for the single doses being used in this protocol.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
	Investigational Product (IP) [DTG and 3TC] Refer to IB for additional information	
DTG: Hypersensitivity reaction (HSR) and rash	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	• *Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2)* • *Specific/detailed toxicity management guidance is provided for HSR and rash (Section 12.7).* • *For Grade 3/4 rash, subjects must permanently discontinue study drug and be withdrawn from the study (Section 5.4.3)* • *The subject informed consent form includes information on this risk and the actions subjects should take in the event of an HSR or associated signs and symptoms.*
DTG & 3TC: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy (ART) containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries. **3TC:** Current treatment guidelines Department of Health and Human Services, 2013 and European AIDS Clinical Society, 2012) do not recommend monotheraphy with 3TC for patients with HBV infection. Additionally, discontinuation of 3TC in HBV coinfected subjects can result in severe exacerbations of HBV.	*Subjects meeting either of the following criteria during the screening period are excluded (Section 5.2).* • *Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).* • *Alanine Aminotransferase (ALT) or bilirubin >1.5x upper limit of normal (ULN).* • *Subjects positive for HBV (hepatitis B virus surface antigen positive [+HBsAg] or positive hepatitis B core antibody with a negative HBsAg), or HCV (positive hepatitis C antibody test) within 3 months of the Day 1 study visit.* *Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 12.2).*
DTG and 3TC: Renal function	**DTG:** Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of organic cation transporter 2 (OCT-2). DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	• *Increases in serum creatinine are not expected to have any adverse effect and will reverse during the wash out period after each single dosing of DTG, and; therefore, do not require mitigation for this protocol in this respect of DTG.* • *Due to requirements for dose reduction of 3TC in patients with*

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
	Investigational Product (IP) [DTG and 3TC] Refer to IB for additional information	
	3TC is eliminated by renal excretion and exposure increases in patients with renal dysfunction.	*renal dysfunction, only healthy volunteers will be enrolled and subjects with a creatinine clearance (CrCL) <90 mL/min will be excluded in this study.*
DTG: Creatine Phosphokinase (CPK) elevations	**DTG:** Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	*Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 12.7).*

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity grading for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per Sponsor's standard medical monitoring practices.

4.6.2. Benefit Assessment

This is a study in healthy subjects and as such there is no expected benefit to administration of DTG or 3TC. Participation in this study may contribute to the process of developing new therapies for HIV. There may be benefit to individual subjects from the medical evaluations and assessments that could identify conditions that the subject was previously unaware of.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with DTG and 3TC are justified by the anticipated benefits that may be afforded to subjects with HIV. The events noted in Section 4.6.1 were observed with the repeated doses of DTG and 3TC. The risk of these events would be significantly lower for the single doses being used in this protocol.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV Healthcare investigational product or other study treatment that may impact subject eligibility is provided in respective IBs and product labels.

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

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Between 18 and 55 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac evaluation (history, electrocardiogram [ECG]). 3. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor if required, agree and document that the finding is unlikely

to introduce additional risk factors and will not interfere with the study procedures.

4. Subject must be able to swallow 2 tablets at the same time (Reference tablets only).

WEIGHT
5. Body weight ≥50 kg (110 lbs.) for men and ≥ 45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m2 (inclusive)

SEX
6. Male or Female Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: ○ Documented tubal ligation ○ Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion ○ Hysterectomy ○ Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea; in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 12.5) from 30 days prior to the first dose of study medication and until at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer after the last dose of study medication and completion of the follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
7. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply ply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. ALT and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 3. QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450msec. NOTES: • The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. For purposes of data analysis, QT interval corrected for heart rate according to Bazett's formula (QTcB), QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

CONCOMITANT MEDICATIONS
4. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and ViiV Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS
5. History of regular alcohol consumption within 6 months of the study defined as: An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits. 6. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 1 month prior to screening.

CONTRAINDICATIONS
7. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
8. Creatinine clearance (CrCL) <90 mL/min 9. A positive hepatitis B surface antigen (HBsAg) or a positive hepatitis B core antibody with a negative hepatitis B surface antibody, positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. 10. A positive pre-study drug/alcohol screen. 11. A positive test for HIV antibody. 12. Where participation in the study would result in donation of blood or blood product in excess of 500 mL within 56 days. 13. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.4).

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request

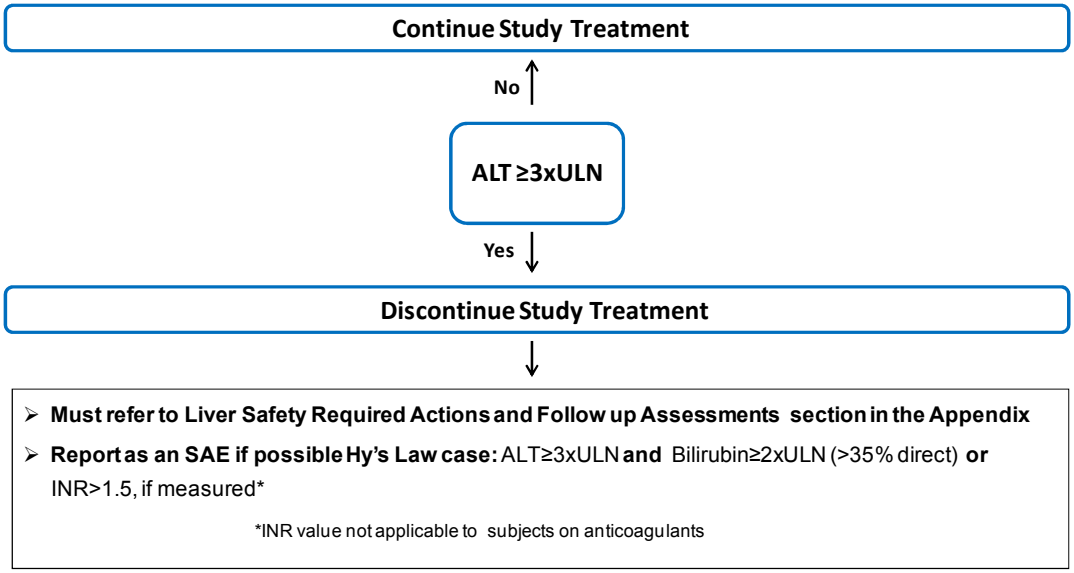
destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2 (Section 12.2).

Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

A subject that meets the criterion below will be withdrawn from the study.

- QTcF > 500 msec

NOTES:

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
- For example, if a subject is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.4.3. Rash

If subject develops Grade 3/4 rash, subject must permanently discontinue study drug and will be withdrawn from the study. Specific/detailed toxicity management guidance is provided for rash in Section 12.7.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may; therefore, refer to the individual study treatments or the combination of those study treatments.

Study Treatment				
	Reference Treatment		**Test: FDC Monolayer Tablet**	**Test: FDC Bi-layer Tablet (if conducted)**
Product name:	Dolutegravir	Lamivudine (EPIVIR)	Dolutegravir/Lamivudine Tablets, 50 mg/300 mg Item Code DP277482 Product Code AH	Dolutegravir/Lamivudine Tablets, 50 mg/300 mg Item Code TBD Product Code TBD
Formulation components:	Dolutegravir, D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, Opadry II white 85F48011	Lamivudine, Microcrystalline cellulose, sodium starch glycolate, magnesium stearate, Opadry Gray YS—1-17506A	Dolutegravir, Lamivudine D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, Aquarias film coat white BP18237	Dolutegravir, Lamivudine D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, magnesium stearate, Aquarias film coat white BP18237
Formulation Description	Clinical image dolutegravir tablet	Commercial EPIVIR Tablet	Commercial dolutegravir granules made at set point conditions combined with extragranular lamivudine and excipients	Information forthcoming
Dosage form:			Tablet	
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	Dolutegravir 50 mg, Lamivudine 300 mg	
Route of Administration	Oral			
Dosing instructions:	One or both, tablet(s) to be taken at the same time with 240 mL of room temperature water			
Physical description:	A white, film-coated, round tablet debossed with SV 572 on one side and 50 on the other side.	Gray, diamond-shaped tablet, engraved “GX EJ7” on one side and plain on the other side.	Oval, biconvex, white, film coated tablet deembossed ‘SV H7I’ on one face	Oval, biconvex, white, film coated tablet deembossed ‘SV 13N’ on one face
Method for individualizing dosage:	One tablet			

6.2. Treatment Assignment

Subjects will be randomized to one of the following two sequences in Part 1 and Part 2, if conducted, in accordance with the randomization schedule generated by GSK Clinical Statistics or designee, prior to the start of the study, using validated internal software.

A description of each regimen is provided in Table 2:

Table 2 Treatment Assignments

Sequences	Period 1	Period 2	Period 3
	Bioequivalence, 2 Period-Crossover Design		Food effect[a]
Part 1			
A/B, n=38	A	B	B Fed (n=16)
B/A, n=38	B	A	
Part 2 (if conducted)			
A/C, n=38	A	C	C Fed (n=16)
C/A, n=38	C	A	

Treatment A = DTG 50 mg tablet (clinical image) plus a single EPIVIR 300 mg tablet
Treatment B = DTG 50 mg/3TC 300 mg FDC monolayer formulation (Product code AH)
Treatment C = DTG 50 mg/3TC 300 mg FDC bilayer formulation (Product code TBD)
a. first 16 subjects who complete the two treatment periods, and consent to continue to complete period 3 in each part

6.3. Planned Dose Adjustments

This study will be conducted using single doses of investigational product. There will be no dose adjustments.

6.4. Blinding

This will be an open-label, randomized, study.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). Information on the Handling of Clinical Testing Samples for Pivotal Bioequivalence Studies is provided in Section 12.3.

- Further guidance and information for final disposition of unused study treatment are provided in the Dispensing plan provided by the site.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from ViiV Healthcare.

6.7. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of dolutegravir >50 mg or lamivudine >300 mg within a 24 hour time period ± 1 hour will be considered an overdose.

ViiV Healthcare does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until DTG and 3TC can no longer be detected systemically (at least 7 days)
3. Obtain a plasma sample for pharmacokinetic (PK) analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (CRF).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from ViiV Healthcare after completion of the study because only healthy volunteers are eligible for study participation.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice (and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices) from 7 days prior to the first dose of study medication until after the collection of the final pharmacokinetic sample after the final dose.

Subjects will refrain from chewing or ingesting sugar-free gums, candies or other processed food/drink products that containing sugar alcohols (e.g., sorbitol, mannitol, xylitol, maltitol, isomalt) during the inpatient period of each dosing session (i.e., Day -1 through 48 hours post-dose).

Once in the clinical unit subjects will not be allowed to eat anything other than the food provided by the study center.

6.10.1.1. Fasting Conditions

In treatment periods 1 and 2 of each part of the study during the overnight period from Day -1 to Day 1:

- An evening meal and/or snack, identical across each period, will be provided by the unit (e.g. on Day -1).
- Subjects must then fast from all food and drink (except water) for 10 hours pre-dose and prior to any clinical laboratory evaluations (except repeat evaluations).
- No food is allowed for at least 4 hours post-dose.
- Room temperature water will be provided with dosing (~240 mL, 8 fluid ounces) and at all times except 1 hour pre-dose through 2-hours post-dose. The full 240 mL must be consumed at dosing.

6.10.1.2. Fed Conditions (Period 3 only)

In Period 3 of each part of the study, subjects will receive study medication following a standard high fat breakfast similar to what is defined in FDA Guidance, 2002. Following an overnight fast of at least 10 hours, subjects will start the recommended meal 30 minutes prior to dosing. Study subjects will eat this meal in 25 minutes or less and dosing will be administered 30 minutes after the start of the meal. Identical breakfasts will be served for this period on the dosing day and the entire meal must be consumed. Dosing will occur with 240 mL (8 fluid ounces) of room temperature water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except 1 hour pre-dose through 2-hours post-dose.

An example high-fat meal would be:

- two eggs fried in butter,
- two strips of bacon,
- two slices of toast with butter,
- four ounces of hash brown potatoes and
- eight ounces of whole milk.

Substitutions to the test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). At all other times, subjects will receive standardized meals scheduled at the same time in each period of the study.

6.10.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic sample during each dosing session.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- Use of tobacco products is not allowed from 1 month prior to screening until after the final follow-up visit.

6.10.3. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests (e.g., screening, Day -1, and follow-up). Subjects will maintain upright position (sitting, walking, or propped upright in bed) for 4 hours post-dose. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Acetaminophen, at doses ≤2 grams/day, is permitted for use at any time during the study. Other concomitant medications may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.

6.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking any other prescription and non-prescription drugs including vitamins, herbal and dietary supplements (including St John's Wort), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit,

unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

7. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
  1. 12-lead ECG
  2. vital signs
  3. blood draws.

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, and pharmacokinetic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK/ViiV study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Table 3 Screening Assessments

Visit Window (relative to Day 1)	Day -30 to -2	Notes
Informed Consent	X	
Demographics	X	
Physical examination height, weight and BMI	X	
Medical/medication/ history	X	*Medical/medication/drug and alcohol history will be recorded at screening, and updated at admission.*
Urine drug / Cotinine and Breathalyzer screening	X	
12-lead ECG and Vital Signs	X	
Serum or urine hCG test (female subjects only)	X	• *See inclusion criterion #6.* • *Performed at site standard procedure.*
FSH and estradiol (women)	X	
HIV, Hep B and Hep C Screen	X	
Hematology/Chemistry/Urinalysis tests	X	

Table 4 Treatment Period Assessments

Assessments	All Dosing Periods							Follow-up	Notes
	Day -1	Day 1			Day 2	Day 3	Day 4		*Day -1 of Periods 2 to 3 may be the same day as Day 6 of prior periods*
		Pre-dose	0 hr	Post Dose	-	48 hr	72 hr		
Admission to Unit	X								
Discharge						X			
Outpatient Visit							X	X	*Follow-up visit will occur 7 to 14 days post last dose.*
12-lead ECG	X								*Single ECGs will be collected at Screening and on Day-1 of Period 1 only. Additional ECGs may be performed at the discretion of the investigator.*
Vital signs	X	X		At 4 hours post-dose	X	X	X	X	*Single measurements performed at all time points.*
Brief Physical Exam	X								• *Brief examinations may be made full examinations and laboratory procedures may be repeated, if needed, at the discretion of the Investigator.* • *Illicit Drug/Alcohol/Cotinine/pregnancy screening will be performed in accordance with the sites' standard practice.* • *Clinical laboratory tests – see Table 5.*
Urine Drug/ Cotinine and Breathalyzer	X								
Pregnancy test	X							X	
Clinical laboratory tests	X							X	
Dosing			**X**						*Subject will be dosed while in the seated position.*
Pharmacokinetic Sampling		X		Collect at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 hours post-dose			X		*Pre-dose (within 15 minutes prior to dosing).* *4 hour post dose sample must be taken prior to provision of food.* *Permitted window for the collection of PK sample at each time point will be specified in BioPacket.*
Meals – (Treatment periods 1 and 2)	Fasted from 10 hours prior to dosing to 4 hours post-dose			Standard for the study center					*See also Section 6.10.1.1*
Meals - Treatment Period 3 (Fed Conditions only)	*Fasted from 10 hours prior to test meal and dosing then through 4 hours post-dose*			*Standard for the study center*					*Entire meal to be consumed in 25 minutes or less and dosing will be administered 30 minutes after the start of the meal. See also Section 6.10.1.2*
Adverse Events	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (e.g., vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4 (see Section 12.4).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK/ViiV product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.1), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK/ViiV within 24 hours, as indicated in Section 12.4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK/ViiV.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK/ViiV are provided in Section 12.4

7.3.1.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Section 12.4.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK/ViiV of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

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

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

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

7.3.2. Pregnancy

Details of all pregnancies in all female subjects will be collected after the start of dosing and until the final post-dose follow-up visit.

If a pregnancy is reported then the investigator should inform GSK/ViiV within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 12.5.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.4. Vital Signs

Vital signs will be measured in the supine or semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure (BP) and pulse rate.

7.3.5. Electrocardiogram (ECG)

12-lead ECGs will be performed with the subject in a supine or semi-supine position having rested in this position for at least 10 minutes beforehand.

Single 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 5, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the BioPacket. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

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

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 5.

Table 5 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	*RBC Indices*	*White blood cell (WBC) count with Differential:*	
	Hematocrit Hemoglobin Red blood cell Count (RBC) WBC Count (absolute)	Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV)	Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Creatine phosphokinase (CPK)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening and/or Additional Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis B core antibody • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Cotinine • Creatinine clearance (CrCL) for GFR estimation • Serum or urine hCG Pregnancy test (as needed for women of child bearing potential)			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 12.2, Appendix 2.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

Further information on the Handling of Clinical Testing Samples in Pivotal Bioequivalence Studies in provided in Section 12.3.

7.4.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of DTG and 3TC will be collected at the time points indicated in Section 7.1 Time and Events Table. The 4-hour post-dose sample must be drawn prior to the subjects' first post-dose meal. The actual date and time of each blood sample collection will be recorded.

For each time point identified in Section 7.1, Time and Events Table, 2 mL of blood will be collected into di-potassium ethylenediaminetetraacetic acid (K_2EDTA) tubes. Details of PK blood sample collection, processing, storage and shipping procedures are provided in the site provided BioPacket.

7.4.2. Sample Processing Procedures

If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, will be kept patent with normal saline, and will be removed after the last blood sample is collected or earlier if the subject requests. To avoid artificial dilution of the PK samples by saline, 1 mL of whole blood will be collected and discarded before each whole blood sample is collected.

Collect each serial whole blood PK sample as close as possible to the planned time relative to dosing detailed in the protocol. Collect a whole blood (2 mL) sample into a properly labelled K_2EDTA evacuated blood collection tube. Record the date and exact time that each sample is collected in the CRF.

7.4.3. Sample Storage Conditions

Immediately after collection, gently invert (DO NOT SHAKE) the blood collection tube 8-10 times to mix the K_2EDTA anti-coagulants with the whole blood and place the samples at room temperature. Within 45 minutes of sample collection, centrifuge for 10 minutes, at 1500 - 2000 G, in 4°C. Within 30 minutes of centrifugation, using a polyethylene pipette, transfer plasma into separate, single, and appropriately labelled 2 mL Amber Sarstedt tubes. Immediately freeze the storage tubes in an upright position at -20°C.

7.4.4. Sample Analysis

Dolutegravir will be extracted from plasma using protein precipitation followed by ultra performance liquid chromatography triple quadrapole mass spectrometry (UPLC-MS/MS) using the previously validated method, Quantitation of GSK1349572 in Human Plasma via UPLC with MS/MS Detection (PPD method number, P1170.02; GlaxoSmithKline Document Number 2012N147635_00. The analysis will be performed by PPD, 3230 Deming Way, Middleton, WI, USA. The DTG sample analysis will be under the management of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Raw data will be archived at the bioanalytical site.

Lamivudine will be extracted from plasma using protein precipitation followed by high performance liquid chromatography triple quadrapole mass spectrometry (HPLC-MS/MS) using the previously validated method, Quantitation of Abacavir and

Lamivudine in Human Plasma via UHLC with MS/MS Detection (PPD method number, P1165; GlaxoSmithKline Document Number 2012N147635_00). The analysis will be performed by PPD, 3230 Deming Way, Middleton, WI, USA. The lamivudine sample analysis will be under the management of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Raw data will be archived at the bioanalytical site.

8. DATA MANAGEMENT

- For this study subject data will be entered into a Site defined and GSK validated eDC system (TrialOne), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK/ViiV policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The first two treatment periods of each part of this study are designed to test the bioequivalence of FDC tablets of DTG and 3TC (test treatment) relative to co-administered DTG plus 3TC (reference treatment) all under fasting conditions. The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, $\mu(test)/\mu(reference)$, for each primary PK endpoint, is either less than 0.800 or greater than 1.250. The alternate hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is greater than or equal to 0.800 and less than or equal to 1.250. Symbolically, this is expressed as follows: H(0): $\mu(test)/\mu(reference) < 0.800$ or $\mu(test)/\mu(reference) > 1.250$, i.e., treatments are not bioequivalent versus H(1): $0.800 \leq \mu(test)/\mu(reference) \leq 1.250$ i.e., treatments are bioequivalent. For each PK parameter designated as a primary endpoint (see Section 3), a two one-sided t-test (TOST) procedure (Schiurmann, 1987) with $\alpha=0.05$ for each one-sided test will be used to test this set of hypotheses. This is equivalent to requiring that a 90% interval for the true ratio of test to reference geometric means falls entirely within the range of 0.800 to 1.250. To declare bioequivalence of FDC tablet DTG and 3TC to co-administered DTG plus 3TC, the primary PK endpoints for both analytes should demonstrate bioequivalence.

For the food effect portions, no formal hypothesis will be tested and an estimation approach will be used to evaluate the effect of food on the FDC tablet.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

For the bioequivalence portions, geometric mean ratio and within subject variability from the PK analysis of a similar FDC formulation in study 204993 (GlaxoSmithKline Document Number 2015N258080_00 are shown in Table 6.

Estimates of the likely CVw% and true GLS means ratio were based on the results of study 204993 (GlaxoSmithKline Document Number 2015N258080_00) and consideration of in vitro dissolution properties for DTG. Based on the largest CVw estimate of 26% (SD=0.256) and the following assumptions, a sample size of 70 statistically evaluable subjects will provide 90% power to demonstrate bioequivalence for the FDC compared to co-administration of DTG and 3TC:

- a true ratio of 1.10,
- the within-subject variability from the current study will not be larger than that used in the sample size calculations,
- data are log-normally distributed, and each one sided t-test is made at the 5% level.

Table 6 Ratio of Geometric Least Squares Means and CVw% for DTG and 3TC in Study 204993

PK Parameters	DTG		3TC	
	Product Code AA vs. Reference	Product Code AB vs. Reference	Product Code AA vs. Reference	Product Code AB vs. Reference
$AUC_{(0-t)}$ (h.µg/mL)	1.126 (25.6)	1.014 (25.6)	1.024 (9.6)	1.042 (9.6)
$AUC_{(0-\infty)}$ (h. µg/mL)	1.122 (25.4)	1.015 (25.4)	1.033 (9.0)	1.030 (9.0)
Cmax (µg/mL)	1.145 (25.7)	1.020 (25.7)	1.178 (19.9)	1.231 (19.9)

For the food effect portions, based on a CVw of 26% and a sample size of 14 evaluable subjects for food effect assessment, it is estimated that the precision (i.e., half width of the 90% confidence interval on the log scale) for the treatment difference will be within 17.2% of the point estimate for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}, for food effect assessment.

9.2.2. Sample Size Sensitivity

A sensitivity analysis was conducted in the event that the variability will be greater than estimated or the GLS means ratio deviates from assumptions for the bioequivalence portions. The effects on the power of declaring bioequivalence in the face of either a change of magnitude in the within subject variation or a shift in the expected ratio of the means are examined and presented in Table 7 for both DTG and 3TC. A sample size of 70 evaluable subjects will provide approximately 79% or 52% power to demonstrate bioequivalence in 3TC C_{max} for the FDC compared to co-administration of DTG and 3TC, if CVw is 20% and the true ratio is as high as 1.15 or 1.18; respectively, in 3TC C_{max}. This higher 3TC C_{max} is not considered clinically significant and does not represent a safety concern.

Table 7 Within-Subject Variability and Changes in Expected True Ratio of Test: Reference on Power with the Targeted Sample

Analyte	Target Sample Size	Within Subject Variability (CVw%)	True Ratio	Power (%)
DTG	70	26	0.95	98.9
			1.02	99.9
			1.05	99.1
			1.10	90.0
			1.15	60.4
	70	30	0.95	96.3
			1.02	99.1
			1.05	96.7
			1.10	81.8
			1.15	50.8
	60	26	0.95	97.7
			1.02	99.6
			1.05	98.0
			1.10	85.6
			1.15	54.8
	60	30	0.95	93.6
			1.02	98.0
			1.05	94.1
			1.10	76.2
			1.15	45.7
3TC	70	20	1.10	98.4
			1.15	79.4
			1.18	52.4
	70	25	1.10	91.9
			1.15	63.3
			1.18	39.2
	60	20	1.10	96.8
			1.15	73.7
			1.18	47.2
	60	25	1.10	87.8
			1.15	57.5
			1.18	35.3

For the food effect portions, a higher within-subject CVw of 30% will be assumed. With 14 evaluable subjects, it is estimated that the half width of the 90% confidence interval for the treatment difference on the log scale will be within 19.8% of the point estimate for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and C_{max}.

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Subjects excluded from any analyses will be fully documented and justified within the clinical study report. All analyses will be based on the actual treatment that each subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the clinical study report

The following populations will be used for the analysis and reporting of data:

Screening Population

All subjects who signed the consent form will be included in this population. This population will be used to present the date of first subject first screened, and numbers of subjects screened and enrolled.

Safety Population

All subjects who enrolled in the study and received at least one dose of study drug will be included in the Safety Population. This will be the population for the safety analyses and for summarization of baseline/demographic characteristics.

Pharmacokinetic Plasma Concentration Population

The PK Plasma Concentration Population will include all subjects who undergo plasma PK sampling and have evaluable PK assay results for DTG or 3TC. This population will be used for Listing the PK concentrations, calculating PK parameters, and plotting of the individual concentration-time profiles for DTG and 3TC. Data from subjects who vomit within 4 hours of study drug administration will be excluded from pharmacokinetic concentration summary, pharmacokinetic parameter summary, and statistical comparisons, but will be included in the Listings.

Pharmacokinetic Parameter Summary Population

The PK Parameter BE Summary Population will include all subjects who have evaluable PK parameters for both analytes and for both Period 1 and Period 2. Data from subjects who vomit within 4 hours of study drug administration will not be considered as evaluable. This population will be used for the statistical analysis of parameter data, the PK concentration summary, and the PK parameter summary and figures for DTG and 3TC for bioequivalence assessment. Excluded subjects will be included in footnotes for summary tables.

The PK Parameter Food Effect Summary Population will include subjects who participate in the food effect part of study, and have evaluable PK parameters for both fed and fasted administration of the FDC tablet formulation. Data from subjects who vomit within 4 hours of study drug administration will not be considered as evaluable. This population will be used for summary and analysis of PK parameter data for food effect assessment.

9.3.2. Interim Analysis

Following completion of Part 1, preliminary PK data from Part 1 will be analyzed. The point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment (monolayer) to the geometric mean of the reference treatments, μ(test)/μ(reference) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} for both DTG and 3TC. The result will be used for planning a future Phase III study.

An independent statistical and programming team will perform the preliminary PK analysis. As the PK data are analyzed separately for each part of the study, there will be no adjustments for multiplicity.

9.4. Key Elements of Analysis Plan

Final analyses will be performed after the completion of the study and final datasets authorization.

Data will be listed and summarized according to GlaxoSmithKline reporting standards where applicable. Listings will be sorted by subject, period, day, and time, noting treatment. Summaries will be presented by treatment, day and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, minimum, maximum; whereas, n and percent will be used as summary statistics for categorical variables; Geometric mean with associated 95% confidence interval (CI), and the between-subject CV (%CVb) for the geometric mean will be included for the PK variables, where applicable.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.3 or higher of the Statistical Analysis Software (SAS) system will be used to analyze data as well as to generate tables, listings, and figures. Complete details will be documented in the RAP.

9.4.1. Primary and Secondary Analyses

Comparisons will be made for the single dose PK parameters of DTG and 3TC, as described in Table 8.

Table 8 Primary and Selected Secondary Comparisons of Interest

	DTG or 3TC PK Parameter	Test	Reference	Assessment
Primary	$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max},	Treatment B	Treatment A	Bioequivalence
		Treatment C (if Part 2 is conducted)	Treatment A	
Secondary	CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$	Treatment B	Treatment A	Bioequivalence

	DTG or 3TC PK Parameter	Test	Reference	Assessment
		Treatment C (if Part 2 is conducted)	Treatment A	
	$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$	Treatment B Fed	Treatment B Fasted	Food Effect
		Treatment C Fed (if Part 2 is conducted)	Treatment C Fasted	

9.4.2. Pharmacokinetic Analyses

PK analyses will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK or their designee. Plasma DTG and 3TC concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, $t_{1/2}$, t_{lag}, C_{24}, λz, $\%AUC_{ex}$, Vz/F, t and CL/F.

PK data will be listed and may be presented in graphical form and will be summarized descriptively. All PK data will be stored in the Archives, GlaxoSmithKline R& D.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline or their designee.

The PK parameters for DTG and 3TC (except t_{max} and t_{lag}) will be log_e-transformed and separately analyzed using a mixed effects model. For the analysis of bioequivalence, the model will include fixed effect terms for period and treatment. Subject will be treated as a random effect in the model. For the analysis of food effect, the model will include a fixed effect term for treatment (fed versus fasted) and a random effect term for subject. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments for the treatment comparisons specified in Section 9.4.1. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of PK parameters between test and reference treatments.

T_{max} and T_{lag} of DTG and 3TC will be separately analyzed with the non-parametric Wilcoxon matched pair method to compute point estimates and associated 90% confidence intervals for the median differences between test and reference treatments.

9.4.3. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the Reporting and Analysis Plan.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK/ViiV will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK/ViiV policy.

The study will also be conducted in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is

being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK/ViiV may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK/ViiV reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK/ViiV determines such action is needed, GSK/ViiV will discuss the reasons for taking such action with the investigator or the head of the medical institution (where

applicable). When feasible, GSK/ViiV will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK/ViiV will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK/ViiV will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK/ViiV audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK/ViiV of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK/ViiV site or other mutually-agreeable location.

GSK/ViiV will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK/ViiV Policy.

11. REFERENCES

FDA Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. 2002.

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GlaxoSmithKline Document Number 2012N145882_00. "Study ING114580 - An Evaluation of the Bioequivalence of a Combined Formulated Tablet (50mg/600mg/300mg dolutegravir/abacavir/lamivudine) Compared to One Dolutegravir 50mg Tablet and One EPZICOM (600mg/300mg abacavir/lamivudine) Tablet Administered Concurrently and the Effect of Food on Bioavailability of the Combined Formulation in Healthy Adult Subjects." Effective Date May 2013.

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GlaxoSmithKline Document Number RM2002/00116/00. An Evaluation of the bioequivalence of a Combined Formulated Tablet (600 mg /300 mg abacavir/lamivudine) Compared to ZIAGEN† (abacavir) 2 X 300mg Tablets and EPIVIR† (lamivudine) 2 X 150mg Tablets Administered Concurrently and the Effect of Food on Absorption of the Combined Formulation in Healthy Adult Subjects. Effective Date June 2002.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR ™
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
$AUC_{(0\text{-}24)}$	Area under the concentration-time curve from time 0 to 24 hours
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve from time 0 to the last measurable timepoint
$AUC_{(0\text{-}\infty)}$	Area under the concentration-time curve from time 0 extrapolated to infinity
BMD	Bone mineral density
BMI	Body mass index
BP	Blood Pressure
BPAP	Bilevel positive airway pressure
BUN	Blood urea nitrogen
C_t	Last measurable drug concentration
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CI	Confidence interval
CL/F	Apparent oral clearance
C_{max}	Maximal drug concentration
CNS	Central nervous system
C_{24}	Drug concentration at 24 hours post-dose
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CPK	Creatine Phosphokinase
CRF	Case report form
CrCl	Creatinine Clearance
CV	Coefficient of Variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug Induced Liver Injury
dL	Decilitre
DNA	Deoxyribonucleic acid
DTG	Dolutegravir, TIVICAY™
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	Fixed dose combination
FRP	Females of reproductive potential
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLS	Geometric least square
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen

HBV	Hepatitis B Virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C Virus
HIV-1	Human Immunodeficiency Virus type 1
HPLC	High-performance liquid chromatography
HRT	Hormone replacement therapy
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INI	Integrase inhibitor
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IEC	Independent Ethics Committee
K_2EDTA	Di-potassium ethylenediaminetetraacetic acid
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LLN	Lower limit of normal
L-TP	Lamivudine triphosphate
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitre
MSDS	Material Safety Data Sheet
NRTI	Nucleoside reverse transcriptase inhibitor
OCT-2	Organic Cation Trasporter-2
PICTS	Phase I Clinical Trial System
PK	Pharmacokinetic
PT	Prothrombin Time
PTT	Partial thromboplastin time
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SJS	Stevens-Johnson Syndrome
SRM	Study Reference Manual
t	Time of last measurable concentration
$t_{1/2}$	Half-life
tl_{ag}	Absorption lag time
T_{max}	Time to observed maximal drug concentration
TEN	Toxic Epidermal Necrolysis
μg	Microgram
ULN	Upper Limit of Normal
UPLC-MS/MS	Ultra performance liquid chromatography triple quadrapole mass spectrometry

US	United States
WBC	White Blood Cell
WHO	World Health Organization

ViiV Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM
TIVICAY
TRIUMEQ
TRIZIVIR

Trademarks not owned by ViiV Healthcare
MedDRA
SAS
WinNonlin

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or International Normalized Ratio (INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Report the event to GSK/ViiV within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, Aspartate Aminotransferase (AST), alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours of last dose.
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
• Serum acetaminophen adduct High-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009].
• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.</td></tr>
</table>

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C Ribonucleic Acid (RNA); Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

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12.3. Appendix 3: Handling of Clinical Testing Samples in Pivotal Bioequivalence Studies

The follow are responsibilities of the Investigator of the Study Site:

- Ensure that a quantity of the clinical testing samples (e.g., study drug product and study drugs to be retained as reserve samples), sufficient to conduct the study, is randomly (nonsystematically) selected from the drug shipment. The remaining testing study drugs must be retained as reserve samples.

- Ensure that an adequate record is maintained of the receipt and distribution of all testing samples on the Drug Accountability forms.

- Storage of the study drugs to be retained as reserve samples is the responsibility of the Investigator and under no conditions can the reserve samples be returned to the Sponsor for storage.

- Ensure that the study drugs to be retained as reserve samples are stored in the original primary packaging and outer cartons. The carton must be closed using tamper-evident tape, and an additional label affixed to the outer carton indicating "Reserve Sample for ViiV/GlaxoSmithKline Study 204994." The label should have an area for the Investigator or pharmacist to sign and date it and the label must not be placed over any existing label(s).

- Store all study drugs to be retained as reserve samples under the appropriate environmental conditions. For products requiring refrigeration or freezing, and for sites located in areas with extreme climate, the temperature must be controlled and a weekly temperature log must be maintained. The storage area must be segregated from the area where the clinical study was conducted and should be limited to access by authorized personnel only.

- Ensure that the reserve samples are retained for a period of at least 5 years following the date on which the application or supplemental application is approved. In the case of non-approval, the retention period is at least 5 years following the date of completion of the corresponding study.

- Consult with the Sponsor if the storage of the study drugs to be retained as reserve samples presents problems.

- Contract with an independent third party to provide storage for study drugs to be retained as reserve samples if storage at the study site is not possible. Before the transfer of the study drugs to be retained as reserve samples, the Sponsor must assess and approve the facilities of the third party.

- The independent third party must store the study drugs to be retained as reserve samples under the appropriate environmental conditions. For products requiring refrigeration or freezing, and for sites located in areas with extreme climate, the temperature must be controlled and a weekly temperature log must be maintained.

- Transfer the study drugs to be retained as reserve samples to an independent third party for storage if the Investigator or study site ceases business.

- When an independent third party stores reserve samples, provide the Sponsor with the name and address of the facility and a contact name and telephone number. Provide the independent third party with a contact name and number for the Sponsor.

- Upon request from the United States Food and Drug Administration (FDA), release the study drugs retained as reserve samples to the FDA and provide the FDA with a written assurance that the reserve samples came from the same supplies used to conduct the specific bioavailability or bioequivalence study.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. • Only laboratory abnormalities that are clinically significant need to be graded as AEs/SAEs. Clinically significant laboratory abnormalities captured as AEs should be graded as per the clinical AE grade criteria, rather than by laboratory grade. Otherwise, laboratory abnormalities that are assessed by the site as not clinically significant (Section 7.3.6) should not be captured as AEs, and are to be graded by the central laboratory or central statistical analysis group using DAIDS laboratory grading criteria (Section 12.5.1).

Events meeting AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Events NOT meeting definition of an AE include:
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK/ViiV in lieu of completion of the GSK/ViiV, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK/ViiV. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK/ViiV. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.4. Evaluating AEs and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities • Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the pre-defined

Assessment of Intensity
outcomes as described in the definition of an SAE. IMPORTANT – PLEASE NOTE THE FOLLOWING STATEMENT: For this study the above criteria regarding mild, moderate and severe will be used in combination with the Modified Division of Acquired immune deficiency syndrome (AIDS) Table for Grading Severity of Adult Adverse Experiences, December 2004 (Section 12.5.1).

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK/ViiV. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK/ViiV.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK/ViiV to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK/ViiV with a copy of any post-mortem

Follow-up of AEs and SAEs
findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK/ViiV within the designated reporting time frames.

12.4.5. Reporting of SAEs to GSK/ViiV

SAE reporting to GSK/ViiV via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK/ViiV will be the electronic data collection tool. • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax/email it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the Electronic Case Report Form (eCRF) page. • After the study is completed at a given site, the electronic data collection tool (e.g., Phase I Clinical Trial System (PICTS)) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

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

1. Intrauterine device or intrauterine system
2. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.
3. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK/ViiV within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK/ViiV. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to

GSK/ViiV as described in While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication and be withdrawn from the study

12.5.3. References

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12.6. Appendix 6 - Division of AIDS Table for Grading The Severity Of Adult And Pediatric Averse Events Version 2.0, November 2014

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention not indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
CARDIOVASCULAR				
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] **Hypertension** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia **Report only one and specify location**	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
MUSCULOSKELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	Bone mineral density (BMD) t-score -2.5 to -1	NA	NA	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< *30 years of age*	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ *30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< *30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute Central nervous system (CNS) Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* ≥ *18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< *18 years of age* *(includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted
RESPIRATORY				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., Continuous positive airway pressure [CPAP], Bilevel positive airway pressure [BPAP], intubation)
SENSORY				
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
SYSTEMIC				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[12] *> 5 to 19 years of age*	NA	World Health Organization (WHO) BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
URINARY				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SITE REACTIONS TO INJECTIONS AND INFUSIONS				
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
LABORATORY VALUES Chemistries				
Acidosis	NA	pH ≥ 7.3 to < Lower limit of normal (LLN)	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin[14], High* *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, Low (mg/dL; *mmol/L*) ≥ *7 days of age*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 < *1.53*
< *7 days of age*	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 < *1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 < *LLN to 1.0*	3.6 to < 4.0 *0.9 to* < *1.0*	3.2 to < 3.6 *0.8 to* < *0.9*	< 3.2 < *0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or Estimated glomerular filtration rate (eGFR), Low *Report only one*	NA	< 90 to 60 mL/min or mL/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 mL/min or mL/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 mL/min or mL/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to* < *6.95*	> 125 to 250 *6.95 to* < *13.89*	> 250 to 500 *13.89 to* < *27.75*	> 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to* < *8.89*	> 160 to 250 *8.89 to* < *13.89*	> 250 to 500 *13.89 to* < *27.75*	> 500 ≥ *27.75*
Glucose, Low (mg/dL; *mmol/L*) ≥ *1 month of age*	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to* < *3.05*	30 to < 40 *1.67 to* < *2.22*	< 30 < *1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** ≥ *18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 ≥ *7.77*	NA
< *18 years of age*	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 ≥ *7.77*	NA
Low Density Lipoprotein (LDL), Fasting, High ≥ *18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 ≥ *4.90*	NA
> *2 to < 18 years of age*	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 ≥ *4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) > *14 years of age*	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< *1 year of age*	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Absolute cluster of differentiation 4 (CD4+) Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age* *(not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
Partial thromboplastin time (PTT), High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 < *25.000 x 10^9*
Prothrombin time (PT), High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 109 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
URINALYSIS				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. Bone mineral density (BMD) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7. Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as Grade 2, if <10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sexes are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

12.7. Appendix 7: Toxicity Management

ANEMIA

Grade 1 (mild) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 1 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, subjects may continue study medication. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, subjects will permanently discontinue study medication and be withdrawn from the trial. Subjects should be followed up until resolution of anemia.

Grade 2 (moderate) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 2 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, subjects may continue study medication. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, subjects will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Hematologist should be considered. Subjects should be followed up until resolution of anemia.

Grade 3 (severe) or Grade 4 (potentially life threatening) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 3 or 4 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin
3. haptoglobin
4. reticulocyte count

Subjects will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Hematologist should be considered. Subjects should be followed up until resolution of anemia.

TOTAL BILIRUBIN ELEVATION

Grade 1 (mild) bilirubin elevation (1.1 - 1.5 times ULN) or Grade 2 (moderate - 1.6-2.5 times ULN):

Any bilirubin value above the upper limit of normal must be repeated and fractionated (direct and indirect bilirubin). Subjects may continue study medication. Subjects should be followed up until resolution (return to baseline) of elevation.

Grade 3 (severe – 2.6-5.0 times ULN) or 4 (life-threatening - > 5.0 times ULN) bilirubin elevation:

Any bilirubin value above the upper limit of normal must be repeated and fractionated (direct and indirect bilirubin). Subjects will permanently discontinue study medication and be withdrawn from the trial. Subjects should be followed up until resolution (return to baseline) of bilirubin elevation.

AST AND ALT ELEVATION

See Section 12.2.

RASH

Grade 1 rash (Localized macular rash):

Subjects with Grade 1 rash should be evaluated by the Investigator immediately. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 rash may continue the study drug at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

Grade 2 rash (Diffuse macular, maculopapular, or morbilliform rash OR Target lesions):

Subjects with Grade 2 rash should be evaluated by the Investigator immediately. Digital photographs should be obtained. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 rash may continue the study drug at the discretion of the Investigator. It should be noted that oral mucosal **erosions** may be part of a Grade 2 rash. Any mucosal **ulceration** increases the severity of the rash to at least Grade 3. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

Grade 3 rash (Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site):

Subjects with a Grade 3 rash will permanently discontinue the study medication. The subject should be evaluated in the physician's office immediately and should be seen in the physician's office or contacted by phone every 2 days until the rash resolves. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

Grade 4 rash (Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)):

Subjects with a Grade 4 rash will permanently discontinue the study medication. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Sponsor and ViiV Healthcare Medical Monitor should be notified of this serious adverse event within 24hr via phone or fax. The subject should be closely followed every day until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis without rash):

Subjects with Grade 1 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 allergic reaction may continue the study drug at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

Grade 2 allergic reaction (Localized urticaria):

Subjects with Grade 2 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 allergic reaction may continue the study drug at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3.

Grade 3 allergic reaction (Generalized urticaria or angioedema):

Subjects will permanently discontinue the study medication and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):

Subjects will permanently discontinue the study medication and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised AIDS Clinical Trials Group (ACTG) Toxicity Grade	Definitions	Investigator Action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria, Angioedema	Discontinue Therapy
Grade 4	Anaphylaxis	Discontinue Therapy

CREATINE PHOSPHATE (CPK) ELEVATION

Grade 3 or higher:

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study drug, study drug should be discontinued and the subject withdrawn from the study.

12.8. Appendix 8 - Country Specific Requirements

No country-specific requirements exist.