TITLE PAGE

Protocol Title: A 2-Part, Phase I, Single Dose, Crossover Relative Bioavailability Study of Both TIVICAY 10 mg Conventional Tablets and 5 mg Dispersible Tablets Compared to Conventional TIVICAY Tablets in Healthy Adult Subjects

Protocol Number: 205893

Short Title: Relative Bioavailability Study of Pediatric Formulations in Healthy Adult Subjects

Compound Number: GSK1349572

Sponsor Name and Legal Registered Address:

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

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1. SYNOPSIS

Protocol Title: A 2-Part, Phase I, Single Dose, Crossover Relative Bioavailability Study of Both TIVICAY 10 mg Conventional Tablets and 5 mg Dispersible Tablets Compared to Conventional TIVICAY Tablets in Fasted Healthy Adult Subjects

Short Title: Pediatric Relative Bioavailability Study in Healthy Adult Subjects

Rationale

TIVICAY (dolutegravir [DTG], GSK1349572) 50mg conventional tablet is for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents. Recently two lower pediatric strength conventional tablets (10mg and 25mg) were approved in the United States (US) and received a positive opinion in the European Union (EU). A dispersible tablet formulation (5 milligram [mg] tablet for oral suspension) of TIVICAY has been developed for administration in younger pediatric populations. This study will be conducted in 2 separate parts with separate groups of fasted healthy adult subjects to investigate both 10 mg conventional tablets (Part 1) and 5 mg dispersible tablets (Part 2). Part 1 of the study will compare the relative bioavailability (BA) of five 10 mg conventional tablets (test) to that of one 50-mg conventional tablet (reference) in one group of subjects. Part 2, will be a pharmacokinetic (PK) evaluation of 5 mg DTG dispersible tablets compared to the conventional 25 mg tablet of TIVICAY taken with water. The randomized cross-over treatments in Part 2 are: 1) 5 mg dispersible DTG tablet (5 tablets) administered as a *dispersion* and immediately taken (test 1), 2) 5 mg dispersible DTG tablet (5 tablets) administered as *direct to mouth* (test 2), and 3) the conventional 25-mg DTG tablet administered as direct to mouth (reference).

Objectives and Endpoints

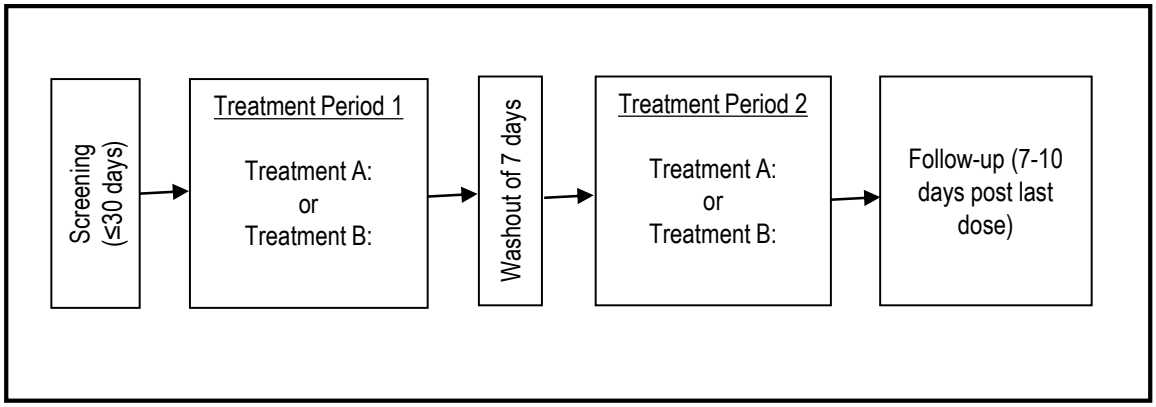
Part 1	
Objective	**Endpoint**
Primary	
To evaluate the relative BA of DTG conventional 10 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 50 mg tablet (reference) administered direct to mouth.	Plasma DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}
Secondary	
• To compare the single dose PK of DTG conventional 10 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 50 mg tablet (reference) administered direct to mouth.	• Plasma DTG 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 safety and tolerability of DTG conventional 10 mg (5 tablets) administered direct to mouth as compared to the administration of a conventional 50 mg tablet (reference) administered direct to mouth.	• Safety and tolerability parameters as assessed by change from baseline in number of subjects with adverse events and toxicity grading of clinical laboratory tests

Part 2	
Primary	
To evaluate the relative BA of DTG dispersible 5 mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	Plasma DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}
Secondary	
• To compare the single dose PK of DTG dispersible 5 mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5-mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	• Plasma DTG 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 safety and tolerability of DTG dispersible 5-mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5-mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	• Safety and tolerability parameters as assessed by change from baseline in number of subjects with adverse events and toxicity grading of clinical laboratory tests
Exploratory	
To evaluate the palatability of the dispersible tablets.	Palatability Questionnaire

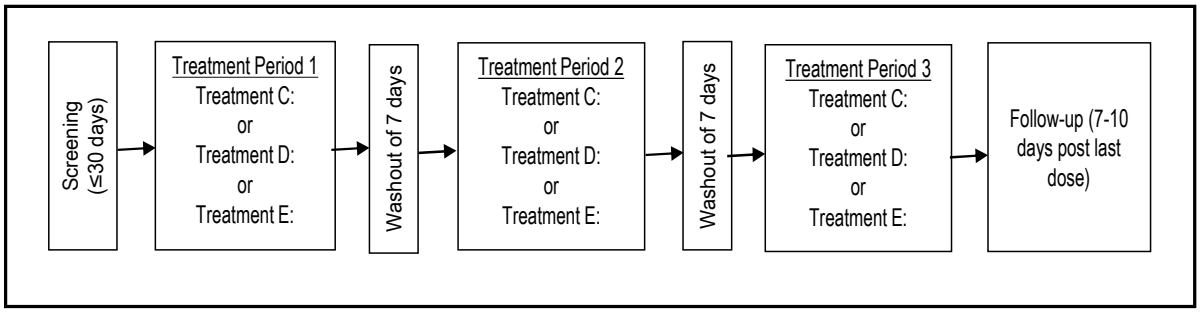
Study Design

This study will be conducted as a 2-part, open-label, randomized, cross-over design with one group of subjects in Part 1 of the study randomized to receive each of 2 study treatments (A and B) over 2 dosing periods, and another group of subjects in Part 2 of the study randomized to receive each of 3 study treatments (C, D, and E) over 3 dosing periods. Subjects will participate in only one part of the study. Parts 1 and 2 of the study may be conducted concurrently. There will be a washout of at least 7 (-4 hours) days between doses of study medication.

Study Design – Part 1 of the Study



Study Design – Part 2 of the Study



Treatment Groups and Duration

The study treatments to be administered in Part 1 of the study are:

- Treatment A: Conventional 10 mg DTG tablet (5 tablets, test) administered direct to mouth.
- Treatment B: Conventional 50 mg DTG tablet (reference) administered direct to mouth

Part 1 – Two-Period Crossover

Sequence (Total N=14)	Period 1	Period 2
1 (n=7)	A	B
2 (n=7)	B	A

The study treatments to be administered in Part 2 of the study are:

- Treatment C: 5 mg dispersible DTG tablet (5 tablets) administered as a dispersion and immediately taken (test 1).
- Treatment D: 5 mg dispersible DTG tablet (5 tablets) administered as *direct to mouth* (test 2).
- Treatment E: Conventional 25 mg DTG tablet administered as direct to mouth (reference).

Part 2 – Three-Period Crossover

Sequence (Total N=24)	Period 1	Period 2	Period 3
1 (n=4)	C	D	E
2 (n=4)	D	E	C
3 (n=4)	E	C	D
4 (n=4)	C	E	D
5 (n=4)	D	C	E
6 (n=4)	E	D	C

The total duration of participation for a subject participating in Part 1 of the study will be approximately 7 to 8 weeks, and for a subject participating in Part 2 of the study, the total duration will be 8 to 9 weeks.

Each participant will have a screening visit within 30 days prior to the first dose of study drug, two treatment periods each for a subject participating in Part 1 of the study and three treatment periods each for a subject participating in Part 2 of the study, with a single dose of study drug per treatment period and a follow-up visit within 7-10 days after the last dose of study drug. At Follow-up, male subjects with no ongoing adverse events (AEs) or Vital Sign/Laboratory measures of clinical concern may be followed virtually by the site via telephone contact.

To ensure adequate washout, there will be at least 7 days between dosing periods, with an allowance window of 4 hrs (i.e., 7 days minus 4 hrs) to allow for flexibility in scheduling subjects to dose at the clinic.

PK samples will be collected for 72 hrs after each dose of study drug.

Number of Participants

Approximately 14 subjects (to achieve 12 completed subjects) will participate in Part 1 of the study, and approximately 24 subjects (to achieve 18 evaluable subjects) will participate in Part 2 of the study. A subject will participate in only one part of the study. If participants prematurely discontinue the study for reasons other than AE, additional replacement participants may be assigned to the same treatment group sequence at the discretion of the Sponsor in consultation with the investigator.

Analysis

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK or their designee. Plasma DTG 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 PK parameters will be determined, as data permit: $AUC_{(0-\infty)}$, area under the plasma concentration-time curve from time of dose to last measurable concentration ($AUC_{(0-t)}$), area under the plasma concentration-time curve from time of dose to 24 hr (AUC_{0-24}), maximum observed concentration (C_{max}), plasma DTG lag time for absorption (t_{lag}), time of occurrence of Cmax (t_{max}), t, terminal elimination phase half-life ($t_{1/2}$), terminal rate constant (λz), %AUCex, apparent oral clearance (CL/F) and apparent volume of distribution during terminal phase (Vz/F), Ct, and concentration at 24 hours after dose administration (C_{24}).

Pharmacokinetic 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 Research and Development (R&D) or their designee.

The PK parameters (except for t_{max} and t_{lag}) for DTG will be log_e-transformed and separately analyzed using a mixed effects model with fixed effect terms for period and treatment for each treatment comparison. Subject will be treated as a random effect in the model. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments. 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.

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.

Palatability questionnaire variables will be summarized descriptively.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening Assessments

Screening procedures (Table 1) may be done over more than one visit but must all be completed within 30 days prior to the first dose of study drug. 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.

Table 1 Screening Assessments

Event	***Notes***
Informed Consent	
Demographics	
Medical history (includes substance usage)	
Inclusion/Exclusion	
HIV, Hep B and Hep C screen	
Drug/alcohol screen	
Brief Physical Exam	
Height, Weight & BMI	
Vital Signs	
12-lead ECG (single)	
FSH and estradiol (women)	
Pregnancy test (serum)	*For Women of Child Bearing Potential (WCBP) only*
Clinical Laboratory Tests (Chemistry, hematology, & urinalysis)	*For Clinical laboratory Tests, see Section 9.3.4*

2.2. Time and Events Table

Table 2 Treatment Period Time and Events

Assessments	All Study Periods (Parts 1 and 2)							Follow-up	***Notes***
	Day -1	Day 1			Day 2	Day 3	Day 4		• *Day -1 of Periods 2 -3 may be the same day as Day 6 of prior periods* • *At Follow-up – Male subjects with no ongoing AEs or Vital Sign/Laboratory measures of clinical concern may be followed virtually by the site via telephone contact.*
		Pre-dose	0 hr	Post Dose	24 hr	48 hr	72 hr		
Admission to Unit	X								
Discharge							X		
Outpatient Visit								X	*Follow-up visit will occur 7 to 10 days post last dose.*
12-lead ECG (single)	X								
Vital signs	X	X			X		X	X	*Single vital sign measurements performed at all time points.*
Brief Physical Exam	X								• *Drug/Alcohol/Cotinine/pregnancy will be performed per the standard practice of the site.* • *Clinical laboratory tests – see* Table 5, Section 9.3.4. • **Clinical laboratory tests at follow-up are only necessary if subject had a previous abnormal lab value*
Urine Drug/Alcohol/Cotinine	X								
Pregnancy test (urine; WCBP)	X							X	
Clinical laboratory tests	X				X			X*	
Dosing			**X**						*See Section 7.1*
Palatability Assessment				Start within 10 min after dose					*Complete for each dispersion treatment C (see Section 12.8, Appendix 8)*
PK Sampling		X		Collect at: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 48 and 72 hrs post-dose.					*Pre-dose (within 15 minutes prior to dosing), Section 9.4*
Meals	Fasted from 10 hrs prior to dosing to 4 hrs post-dose			Standard for the study center					*See also Section 6.3.2 and Section 6.3.3*
Adverse Events / SAE	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

3. INTRODUCTION

3.1. Study Rationale

TIVICAY (dolutegravir [DTG], GSK1349572) 50mg conventional tablet is for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents. Recently two lower pediatric strength conventional tablets (10mg and 25mg) were approved in the United States (US) and received a positive opinion in the European Union (EU). A dispersible tablet formulation (5 milligrams [mg] tablet for oral suspension) of TIVICAY has been developed for administration in younger pediatric populations. This study will be conducted in 2 separate parts with separate groups of fasted healthy adult subjects to investigate both 10 mg conventional tablets (Part 1) and 5 mg dispersible tablets (Part 2). Part 1 of the study will compare the relative bioavailability (BA) of five 10 mg conventional tablets (test) to that of one 50-mg conventional tablet (reference) in one group of subjects. Part 2, will be a pharmacokinetic (PK) evaluation of 5 mg DTG dispersible tablets compared to the conventional 25 mg tablet of TIVICAY taken with water. The randomized cross-over treatments in Part 2 are: 1) 5 mg dispersible DTG tablet (5 tablets) administered as a *dispersion* and immediately taken (test 1), 2) 5 mg dispersible DTG tablet (5 tablets) administered as *direct to mouth* (test 2), and 3) the conventional 25-mg DTG tablet administered as direct to mouth (reference).

3.2. Background

TIVICAY (DTG) as a single drug entity was first approved in the US in August 2013 and is currently approved globally in more than 100 countries. TIVICAY is a next generation integrase inhibitor with low to moderate inter-subject PK variability, a predictable exposure-response relationship, and a 14-hour plasma half-life that supports once-daily dosing without the need for the PK boosters. In addition, DTG lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by HIV-positive patients.

Alternate formulations and dosing strategies (e.g., pediatric granules and dispersible tablets) are being developed for pediatric patients less than 12 years old who may have difficulty swallowing conventional tablet formulations. Since the solubility of DTG is reduced when co-administered with divalent cation-containing products, the relative BA of DTG in dispersible tablets dispersed in either High Mineral Content (Contrex brand mineral water; contains high levels of calcium and magnesium) or Low Mineral Content Water (10% Contrex/90% Purified water) has been evaluated previously. Mineral content had no effect on the relative bioavailability of dispersed tablets (Clinical Investigator's Brochure [GlaxoSmithKline Document Number RM2007/00683/10]).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DTG may be found in the Investigator’s Brochure.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
	Refer to Investigator Brochure (IB) for additional information	
Hypersensitivity reaction (HSR) and rash	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 6.2)* • *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 12.7.4)* • *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.*
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for 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.	*Subjects meeting either of the following criteria during the screening period are excluded (Section 6.2).* • *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).*
Renal function[b]	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 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.*
Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	*Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 12.7.6).*

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.

b. Increases in creatinine of ~0.1 to 0.15mg/dL are expected and will reverse.

3.3.2. Benefit Assessment

This is a study in healthy subjects and as such there is no expected benefit to administration of TIVICAY. 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.

3.3.3. 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 TIVICAY are low.

4. OBJECTIVES AND ENDPOINTS

Part 1	
Objective	**Endpoint**
Primary	
To evaluate the relative BA of DTG conventional 10 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 50 mg tablet (reference) administered direct to mouth.	Plasma DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}
Secondary	
• To compare the single dose PK of DTG conventional 10 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 50 mg tablet (reference) administered direct to mouth.	• Plasma DTG 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 safety and tolerability of DTG conventional 10 mg (5 tablets) administered direct to mouth as compared to the administration of a conventional 50 mg tablet (reference) administered direct to mouth.	• Safety and tolerability parameters as assessed by change from baseline in number of subjects with adverse events and toxicity grading of clinical laboratory tests
Part 2	
Primary	
To evaluate the relative BA of DTG dispersible 5 mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5 mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	Plasma DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}
Secondary	
• To compare the single dose PK of DTG dispersible 5 mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5-mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	• Plasma DTG 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 safety and tolerability of DTG dispersible 5-mg tablets (5 tablets) administered as "disperse and immediately take" and of DTG dispersible 5-mg tablets (5 tablets) administered direct to mouth as compared to a conventional 25 mg tablet (reference) administered direct to mouth.	• Safety and tolerability parameters as assessed by change from baseline in number of subjects with adverse events and toxicity grading of clinical laboratory tests
Exploratory	
To evaluate the palatability of the dispersible tablets.	Palatability Questionnaire

5. STUDY DESIGN

5.1. Overall Design

This study will be conducted as a 2-part, open-label, randomized, cross-over design with one group of subjects in Part 1 of the study randomized to receive each of 2 study treatments (A and B) over 2 dosing periods (see Figure 1), and another group of subjects in Part 2 of the study randomized to receive each of 3 study treatments (C, D, and E) over 3 dosing periods (see Figure 2). Subjects will participate in only one part of the study. Parts 1 and 2 of the study may be conducted concurrently. There will be a washout of at least 7 (-4 hours) days between doses of study medication.

Note: The -4 hours is an allowed tolerance window to the 7 day washout and is to allow the study site and subjects flexibility in scheduling admission and dosing for subsequent treatment periods (i.e., treatment periods 2 and/or 3).

Figure 1 Study Design – Part 1 of the Study

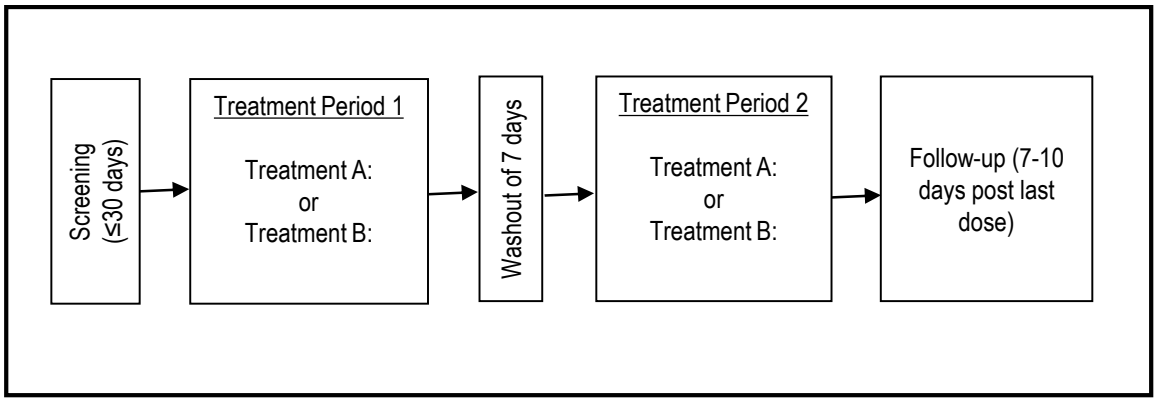
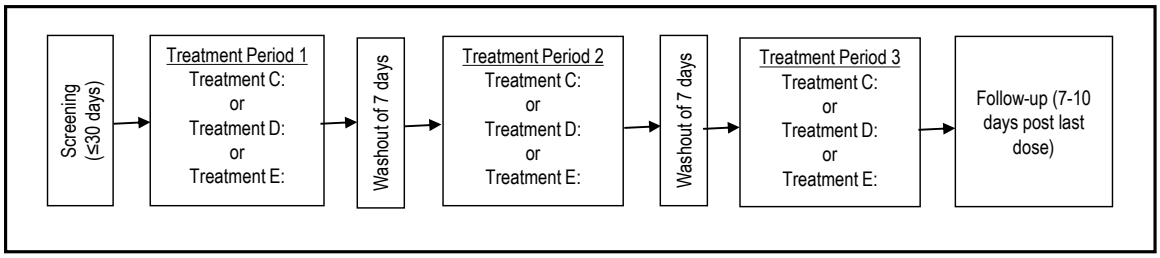


Figure 2 Study Design – Part 2 of the Study



5.2. Treatment Groups and Duration

The study treatments to be administered in Part 1 of the study are:

- Treatment A: Conventional 10-mg DTG tablet (5 tablets, test) administered direct to mouth.
- Treatment B: Conventional 50-mg DTG tablet (reference) administered direct to mouth.

Table 3 Part 1 – Two-Period Crossover

Sequence (Total N=14)	Period 1	Period 2
1 (n=7)	A	B
2 (n=7)	B	A

The study treatments to be administered in Part 2 of the study are:

- Treatment C: 5-mg dispersible DTG tablet (5 tablets) administered as a dispersion and immediately taken (test 1).
- Treatment D: 5-mg dispersible DTG tablet (5 tablets) administered as *direct to mouth* (test 2).
- Treatment E: Conventional 25-mg DTG tablet administered as direct to mouth (reference).

Table 4 Part 2 – Three-Period Crossover

Sequence (Total N=24)	Period 1	Period 2	Period 3
1 (n=4)	C	D	E
2 (n=4)	D	E	C
3 (n=4)	E	C	D
4 (n=4)	C	E	D
5 (n=4)	D	C	E
6 (n=4)	E	D	C

The total duration of participation for a subject participating in Part 1 of the study will be approximately 7 to 8 weeks, and for a subject participating in Part 2 of the study, the total duration will be 8 to 9 weeks.

Each participant will have a screening visit within 30 days prior to the first dose of study drug, two treatment periods each for a subject participating in Part 1 of the study and three treatment periods each for a subject participating in Part 2 of the study, with a single dose of study drug per treatment period and a follow-up visit within 7-10 days after the last dose of study drug. At Follow-up, male subjects with no ongoing adverse events (AEs) or Vital Sign/Laboratory measures of clinical concern may be followed virtually by the site via telephone contact.

To ensure adequate washout, there will be at least 7 days between dosing periods, with an allowance window of 4 hrs (i.e., 7 days minus 4 hrs) to allow for flexibility in scheduling subjects to dose at the clinic.

PK samples will be collected for 72 hrs after each dose of study drug.

5.3. Number of Participants

Approximately 14 healthy subjects (to achieve 12 completed subjects) will participate in Part 1 of the study, and approximately 24 subjects (to achieve 18 evaluable subjects) will participate in Part 2 of the study. A subject will participate in only one part of the study. If participants prematurely discontinue the study for reasons other than AE, additional

replacement participants may be assigned to the same treatment group sequence at the discretion of the Sponsor in consultation with the investigator.

5.4. Participant 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.

5.5. Scientific Rationale for Study Design

This open-label, randomized, cross-over design is well-established for the evaluation of relative bioavailability of different oral dosage forms. Randomization of the treatment sequences is an attempt to prevent bias. The washout of 7 days between dosing periods should eliminate the possibility of carryover of drug exposure from the previous dosing period. In each part of the study, there are appropriately named "test" and "reference" study treatments which will be evaluated for the relative bioavailability comparisons.

The study is subject to the appropriate regulatory approval and Ethics Committee approval, and will be listed on the website ClinicalTrials.gov. No blinding or placebo control will be used, as these are not necessary for the purposes of this study.

5.6. Dose Justification

The US Food and Drug Administration (FDA)-approved dose of DTG for treatment-naive HIV-infected adult and pediatric patients 12 years and older (and ≥40 kilogram [kg]) is 50 mg once daily. The adult dose is given as 1x50 mg tablet once daily.

Part 1 of the study will compare relative BA of five 10-mg conventional tablets (test) to that of one 50-mg conventional tablet (reference). For part 1, the approved adult dose of 50 mg DTG conventional tablet is used as a reference to benchmark exposures with paediatric formulations to what is safe and effective in adults.

Part 2 of the study will compare relative BA of five 5 mg dispersible tablets administered as "disperse and immediately take" and of dispersible 5 mg tablets to be administered as "direct to mouth" to that of a single 25 mg conventional tablet (reference) administered direct to mouth. The 25 mg dose of DTG control dose used in Part 2 of this study will accommodate the relative BA assessment of the two pediatric dosage forms and will require a dosing of only five (5) 5 mg tablets, as opposed to 10 tablets that would have been necessary if the 50 mg DTG control dose would have been chosen for evaluation in Part 2 of the study. With respect to reference dose in Part 2 of this study, the 25 mg tablet is quantitatively proportional to the 50 mg tablet and hence two 25mg tablets are equivalent to 50 mg tablet. However, the 25 mg tablet was chosen as a comparator for this part so as to decrease the burden on the subjects to consume 10 x 5 mg tablets directly to mouth as well as to minimize any associated variability.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

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.

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 the Investigator's Brochure (see GlaxoSmithKline Document Number RM2007/00683/10).

6.1. Inclusion 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 the Investigator's Brochure [GlaxoSmithKline Document Number RM2007/00683/10].

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. Between 18 and 65 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 and electrocardiogram [ECG]). 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 agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
3. Body weight ≥50 kg for males and ≥45 kg for females and body mass index (BMI) within the range 18.5 – 31.0 kg/m^2 (inclusive)

SEX
4. Male or female 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 Appendix 5 [Section 12.5]) from 30 days prior to the first dose of study medication and until 2 weeks after dosing with 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
5. Capable of giving signed informed consent as described in Section 12.3, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QT DURATION CORRECTED FOR HEART RATE [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 correction using Fridericia Formula (QTcF) >450 Milliseconds (msec) NOTES: • The QTcF 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, QTcF, will be used as specified in the Reporting and Analysis Plan (RAP).

CONCOMITANT MEDICATIONS
4. Unable to refrain from the use of prescription (i.e., 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 milliliters [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.

6.3. Lifestyle Restrictions

6.3.1. 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 final dose.

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

6.3.2. Fasting Conditions

During the overnight period from Day -1 to Day 1 of each dosing period:

- An evening meal and/or snack will be provided by the unit (e.g. on Day -1).
- Subjects must then fast from all food and drink (except water) for 10 hrs pre-dose and prior to any clinical laboratory evaluations (except repeat evaluations).
- Water is permitted with dosing (200-250 mL) for all Treatments except Treatment C and at all times except 1 hour (hr) pre-dose through 2-hrs post-dose.
- No food is allowed for at least 4 hrs post-dose.

6.3.3. Fed Conditions

With the exception of the time period outlined for fasting conditions, subjects will receive all other meals as defined as standard for the study center.

6.3.4. Caffeine, Alcohol, and Tobacco

During each treatment period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hrs prior to the start of dosing until collection of the final PK and or pharmacodynamic sample during each session.

During each dosing session, subjects will abstain from alcohol for 24 hrs 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 and until after the final follow-up visit.

6.3.5. Activity

Subjects will abstain from strenuous exercise for 48 hrs prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. A minimal set of screen failure

information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Subjects in Part 1 of the study will be randomized to one of the 2 following treatment sequences: AB or BA in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated software.

Subjects in Part 2 of the study will be randomized to one of the 6 following treatment sequences: CDE, DEC, ECD, CED, DCE, or EDC in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated software.

Descriptions of the study treatments A and B in Part 1 of the study, and study treatments C, D, and E in Part 2 of the study, and the respective treatment sequences are as described in Section 5.1 of this protocol.

Study Treatments in Part 1 of the Study		
Product name:	TIVICAY (DTG)	TIVICAY (DTG)
Dosage form:	Conventional 10 mg DTG Tablet	Conventional 50 mg DTG Tablet
Unit dose strength(s)/Dosage level(s):	Single dose of five (5) 10 mg DTG tablets	Single dose of one (1) 50 mg DTG tablet
Route of Administration	Oral	Oral
Dosing instructions:	**Treatment A:** Take five (5) 10 mg DTG tablets direct to mouth with 240 mL of water	**Treatment B:** Take one (1) 50 mg DTG tablet direct to mouth with 240 mL of water
Physical description:	DTG (10 mg) tablets – White, round, biconvex tablets	DTG (50 mg) tablets – White, round, biconvex tablets
Manufacturer:	GlaxoSmithKline	GlaxoSmithKline
Fasting instructions:	Administer in the AM on an empty stomach. Food will be unavailable until 4h after dose and water until 2h after dose.	Administer in the AM on an empty stomach. Food will be unavailable until 4h after dose and water until 2h after dose.

Study Treatments in Part 2 of the Study		
Product name:	TIVICAY (DTG)	TIVICAY (DTG)
Dosage form:	5 mg Dispersible DTG Tablet	Conventional 25 mg DTG Tablet
Unit dose strength(s)/Dosage level(s):	Single dose of five (5) 5 mg DTG tablets	Single dose of one (1) 25 mg DTG tablet
Route of Administration	Oral	Oral
Dosing instructions:	**Treatment C:** Immediately take five (5) 5 mg Dispersible DTG tablets administered as Dispersed in water **Treatment D:** Take five (5) 5 mg Dispersible DTG tablets with 240 mL of water direct to mouth	**Treatment E:** Take one (1) 25 mg DTG tablet with 240 mL of water direct to mouth
Physical description:	DTG (5 mg) tablets – White, round, biconvex tablets	DTG (25 mg) tablets – White, round, biconvex tablets
Manufacturer:	GlaxoSmithKline	GlaxoSmithKline
Fasting instructions:	Administer in the AM on an empty stomach. Food will be unavailable until 4h after dose and water until 2h after dose.	Administer in the AM on an empty stomach. Food will be unavailable until 4h after dose and water until 2h after dose.

7.1.1. Dosing Dispersible Tablets in Treatment C

Each dispersible tablet for Treatment C contains DTG 5 mg in strength; therefore, 5 tablets will be needed to achieve the 25 mg total dose.

1. Place 25 mL of purified water in a small beaker / container. A 100 mL beaker or a similar-sized vessel works well. A 50 mL syringe is appropriate to measure this volume.
2. Preparation - Place 5 tablets into the beaker and swirl / stir for 3 – 3.5 minutes. The tablets should be fully dispersed in approximately 90 seconds, but swirling/stirring for the full time will guarantee dispersion.
3. Have the volunteer swallow the dispersion as swiftly as they can, preferably in 1 to 2 swallows.
4. Rinse the beaker with 25 mL of purified water, a 50 mL syringe is appropriate to measure this volume, and have the volunteer swallow this as swiftly as they are able, preferably in 1 to 2 swallows.
5. Give the volunteer an additional 190 mL of purified water to swallow.

NOTE: The words “immediately dose” in this protocol mean within one minute after completion of the 3 minute preparation.

Anticipate that there will still be a limited amount of insoluble material visible in the beaker after the dispersion has been dosed and rinsed; this is normal and will not affect the dose delivered.

7.2. Blinding

This is an open-label study; potential bias will be reduced by a randomization of treatments provided to the site pharmacist.

7.3. Preparation/Handling/Storage/Accountability

The tablets are packaged into high-density polyethylene (HDPE) bottles. Each bottle of DTG 50 mg, 25 mg, and 10 mg will contain 30 tablets, and each bottle of DTG 5 mg will contain 60 tablets. Tablets must be stored in the original package with the bottle tightly closed. The bottles contain a desiccant that must be kept in the bottle to protect tablets from moisture.

- 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.
- 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, 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).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual.
- TIVICAY tablets are to be stored at 15-30°C and protected from light. Maintenance of a temperature log (manual or automated) is required.
- 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 GSK.

7.4. Treatment Compliance

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.

7.5. Concomitant Therapy

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.

Use of antacids, vitamins, and iron supplements are strictly prohibited 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 and for the duration of the trial, including follow-up.

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

7.6. Treatment at the End of the Study

This is a single dose study, there will be no treatment at the end of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

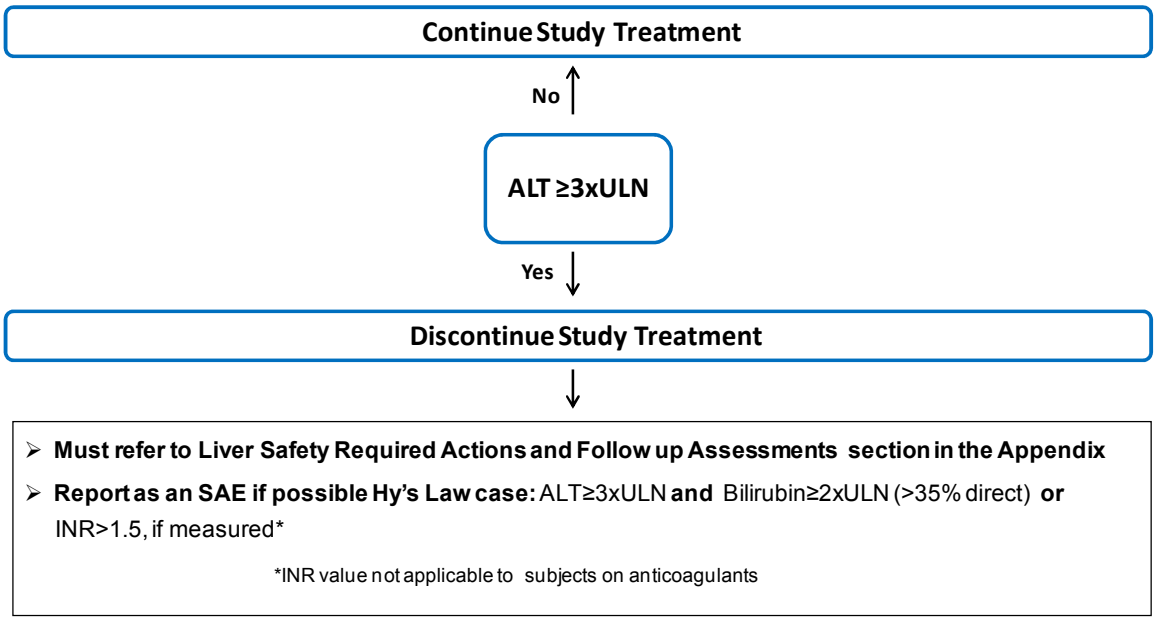
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

NOTE: Although this is a single-dose study, please use the following as 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 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 participant in this study is not allowed.

8.1.2. QTc Stopping Criteria

A subject that meets the following bulleted 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 QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral, compliance or administrative reasons.
- If after screening, the subject requires concurrent medications that cannot be interrupted for 2 weeks prior to administration of investigational product and until completion of the study.
- Pregnancy
- Positive urine drug or alcohol screen.
- Any clinically significant AE deemed to require discontinuation of investigational product.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the Table 2 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 2.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Table 2, are essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in Table 2.

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, PK or other 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 study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/ Independent Ethics Committee (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.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

9.1.1. 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 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 treatment until the follow-up visit at the time points specified in Table 2 (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the electronic case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant 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?”

9.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4 (Section 12.4).

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information, e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure (GlaxoSmithKline Document Number RM2007/00683/10) and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. 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 within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 12.5.2 of Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

In Part 1 of this study, any single dose of DTG >50 mg will be considered an overdose.
In Part 2 of this study, any single dose of DTG>25 mg will be considered an overdose.

ViiV does not recommend specific treatment for an overdose of DTG. 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 AEs)/ SAEs and laboratory abnormalities until DTG can no longer be detected systemically (at least 7 days).
3. Obtain a plasma sample for 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 eCRF.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in Table 2.

9.3.1. Physical Examinations

- A full physical examination, if needed, will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

9.3.2. Vital Signs

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

9.3.3. Electrocardiograms

- 12-lead ECGs will be performed with the subject in a supine or semi-supine position having rested in this position for at least 5 minutes beforehand
- Single 12-lead ECGs will be obtained at screening and on Day -1 as indicated in the Time and Events Table using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. If a subject experiences a QTcF >500 msec, refer to Section 8.1.2 for QTcF withdrawal criteria and repeat 2 ECG recordings over a brief (e.g., 5-10 minute) period (i.e., additional QTcF readings that may be necessary).

9.3.4. 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 in the SoA for the timing and frequency. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. 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 eCRF.

Refer to the Study Reference Manual (SRM)/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[a]	Blood urea nitrogen (BUN)	Potassium	AST (serum glutamic oxaloacetic transaminase [SGOT])	Total and direct bilirubin
	Creatinine	Sodium	ALT (serum glutamic pyruvic transaminase [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 (see Section 2 for timing of these Assessments)	• 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)[b] • Cotinine • Creatinine clearance (CrCL) for glomerular filtration rate (GFR) estimation • Serum or urine human chorionic gonadotropin hCG Pregnancy test (as needed for women of child bearing potential)[b] • The results of each test must be entered into the eCRF.			

NOTES :

[a] Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1 and Section 12.2.

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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 (at the discretion of the Investigator and Medical Monitor). 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.

9.4. Pharmacokinetics

9.4.1. Blood Sample Collection

Blood samples for PK analysis of DTG will be collected at the time points indicated in the Time and Events Table. The actual date and time of each blood sample collection will be recorded. Blood specimens (2 mL) will be collected into K_2 ethylenediaminetetraacetic acid (EDTA) tubes.

Details of PK blood sample collection, Windows of Allowance, processing, storage and shipping procedures are provided in the site provided SRM/BioPacket.

9.4.2. Sample Analysis

Plasma analysis will be performed under the control of Platform Technology and Science (PTS), GlaxoSmithKline, the details of which will be included in the Study Reference Manual (BioPacket). Concentrations of DTG will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM/BioPacket).

Once the plasma has been analyzed for drug concentrations any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS, GlaxoSmithKline protocol.

9.5. Formulation Palatability Assessment

A palatability questionnaire will be administered to each subject in Treatment Arm C within 10 minutes following dosing of dispersion treatments only, see Appendix 8 (Section 12.8). Subjects will be given the questionnaire to read prior to receiving each unique dispersion dose.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

This study is designed to estimate the relative bioavailability of each test treatment to the reference treatment (A vs. B; C vs. E and D vs. E) in both study parts in the fasted state.

No formal hypothesis will be tested. For each pharmacokinetic endpoint (except for time of occurrence of Cmax [t_{max}] and t_{lag}), point estimates and corresponding 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

10.2. Sample Size Considerations

10.2.1. Sample Size Assumptions

Based on the results from a previous PK study of dolutegravir granules administered to healthy volunteers, [GlaxoSmithKline Document Number 2011N124158_00], the within-subject variability (CVw%) of dolutegravir area under the plasma concentration-time curve from time of dose extrapolated to infinity($AUC_{(0-\infty)}$) and maximum observed concentration (C_{max}) ranged from 15.0% to 16.2%. Therefore, it is decided that 16.2% would be a conservative estimate on which the sample size calculation is based.

For Part 1, with a sample size of 12 evaluable subjects (6 subjects/sequence), it is estimated that the precision (i.e. half-width of the 90% confidence interval (CI) on the ratio scale) for the test: reference comparison will be within 13% of the point estimate for $AUC_{(0-\infty)}$ and C_{max}. Hence, if the point estimate of the ratio of geometric means is 1 then the 90% confidence interval (CI) will be approximately (0.89, 1.13).

For Part 2, with a sample size of 18 subjects (at least 3 subjects/sequence), it is estimated that the precision (i.e. half-width of the 90% CI on the ratio scale) for the test: reference comparison will be within 10% of the point estimate for $AUC_{(0-\infty)}$ and C_{max}. Hence, if the point estimate of the ratio of geometric means is 1 then the 90% CI will be approximately (0.91, 1.10).

10.2.2. Sample Size Sensitivity

For the sensitivity analysis, assuming a higher within-subject variability (24%), a sample size of 12 evaluable subjects in Part 1, it is estimated that the half width of the 90% CI for the ratio of treatment comparison (test : reference) would be within 19% of the point estimate for $AUC_{(0-\infty)}$ and C_{max}. A sample size of 18 evaluable subjects in Part 2, it is estimated that the half width of the 90% CI for the ratio of treatment comparison (test:reference) would be within 14% of the point estimate for $AUC_{(0-\infty)}$ and C_{max}.

10.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

10.2.4. 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:

All Subjects Population

The 'All Subjects Population' is defined as all subjects who receive at least one dose of study medication. This population will be used for all demographic and safety summaries.

Pharmacokinetic (PK) Population

The 'PK Population' is defined as subjects in the 'All Subjects' population for whom a PK sample was obtained and had evaluable PK assay results. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded. This population will be used for reporting of PK data.

10.2.5. Interim Analyses

There will be no formal interim analysis.

10.3. Key Elements of Analysis Plan

Final analyses will be performed after the completion of the study and final database 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 variable. Geometric mean with associated 95% CI, and the between-subject coefficient of variance (CV) (%CVb) for the geometric mean will be included for 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 9.4 or higher of the Statistical Analysis Software (SAS) system will be used to analyze data as well as to generate tables, listings, and figures.

10.3.1. Primary Analyses

10.3.1.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK or their designee. Plasma DTG 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 PK parameters will be determined, as data permit: $AUC_{(0-\infty)}$, area under the plasma concentration-time curve

from time of dose to last measurable concentration ($AUC_{(0-t)}$), area under the plasma concentration-time curve from time of dose to 24 hr (AUC_{0-24}), C_{max}, plasma DTG lag time for absorption (t_{lag}), time of occurrence of Cmax (t_{max}), terminal elimination phase half-life ($t_{1/2}$), terminal rate constant (λz), % of $AUC_{(0-\infty)}$ that was extrapolated (%AUCex), apparent oral clearance (CL/F) and apparent volume of distribution during terminal phase (Vz/F), last quantifiable concentration (Ct), and concentration at 24 hours after dose administration (C_{24}).

Pharmacokinetic 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 Research and Development (R&D).

The PK parameters (except for t_{max} and t_{lag}) for DTG will be log_e-transformed and separately analyzed using a mixed effects model with fixed effect terms for period and treatment for each treatment comparison. Subject will be treated as a random effect in the model. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments. 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.

Further details will be provided in the Regulatory Analysis Plan (RAP).

10.3.1.2. 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 RAP.

10.3.2. Palatability Questionnaire

Palatability questionnaire variables will be summarized descriptively. Further details will be provided in the RAP.

11. REFERENCES

GlaxoSmithKline Document Number RM2007/00683/10: GSK1349572 Clinical Investigator's Brochure. 10 October 2016

GlaxoSmithKline Document Number 2011N124158_00. Relative bioavailability study of a tablet formulation vs. pediatric granule formulation of dolutegravir 50 mg and effect of different types of water plus infant formula on the pediatric granule formulation in healthy male and female volunteers (ING114556); February 2012.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase (SGPT)
ART	Antiretroviral Therapy
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time of dose to last measurable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time of dose extrapolated to infinity
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time of dose to 24 hr
%AUCex	% of $AUC_{(0-\infty)}$ that was extrapolated
BA	Bioavailability
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C24	Concentration at 24 hours after dose administration
CI	Confidence Interval
CL/F	Apparent oral clearance
C_{max}	Maximum observed concentration
C_{24}	Observed concentration at 24h post-dose
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CrCL	Creatinine Clearance
CRF	Case Report Form
CV	Coefficient of variance
CVb	Between subject coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug-Induced Liver Injury
DTG	Dolutegravir
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
FDA	Food and Drug Administration
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HRT	Hormone Replacement Therapy
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
OCT	Organic cation transporter
PK	Pharmacokinetic(s)
PTS	Platform Technology and Science
QTc	QT duration corrected for heart rate
QTcF	QT correction using FridericiaFormula
R&D	Research and Development
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOP	Standard Operating Procedure
SRM	Study Reference Manual
$t_{½}$	Terminal elimination phase half-life
TEN	Toxic epidermal necrolysis
t_{lag}	Plasma DTG lag time for absorption
t_{max}	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US / USA	United States (of America)
WBC	White blood cells
WCBP	Women of Child Bearing Potential
Vz/F	Apparent Volume of Distribution During Terminal Phase
λz	Terminal Rate Constant

Trademark Information

Trademarks of the ViiV group of companies
TIVICAY

Trademarks not owned by the ViiV group of companies
WinNonlin
SAS

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	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

Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF, 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, 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	• 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 NR >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 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 eCRF forms.

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 RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

Appendix 2 - References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al.. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. 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 study treatment.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). 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 before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
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 participant'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 participant's condition. Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

> An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk

factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK/ViiV

SAE Reporting to GSK via Electronic Data Collection Tool

The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.

If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).

The site will enter the SAE data into the electronic system as soon as it becomes available.

The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE

entry into the eCRF.

After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

Contacts for SAE reporting can be found in the Medical Monitor Name and Contact Information section of the Title Page of this protocol.

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 [Hatcher, 2011].

1. Contraceptive subdermal implant
1. Intrauterine device or intrauterine system
2. Combined estrogen and progestogen oral contraceptive
3. Injectable progestogen
4. Contraceptive vaginal ring
5. Percutaneous contraceptive patches
6. 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. 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.
7. Male condom plus partner use of one of the contraceptive options below that meets the standard operating procedure (SOP) effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Combined estrogen and progestogen oral contraceptive
    - Injectable progestogen
    - Contraceptive vaginal ring
    - Percutaneous contraceptive patches

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 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. 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 as described in Section 9.1.5. 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 or be withdrawn from the study.

12.5.3. Appendix 5 References

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

12.6. Appendix 6 - Division of AIDS Table For Grading The Severity Of Adult And Paediatric 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 Treatment	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	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 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
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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated 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)
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

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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., CPAP, 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)
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

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

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

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

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

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
> 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*
HEMATOLOGY				
Absolute 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*

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*
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*
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 (page 23).
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. BMD t and z scores can be found in: [Kanis, 2007]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 (page 23).
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 sex 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.

Appendix 6 References

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.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics Dec 2011, 128 (Supplement 5) S213-S256; DOI: 10.1542/peds.2009-2107C.

12.7. Appendix 7: Toxicity Management

12.7.1. 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.

12.7.2. 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.

12.7.3. AST AND ALT ELEVATION

See Section 12.2.

12.7.4. 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 9.1 and Section 9.3.

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 9.1 and Section 9.3.

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 9.1 and Section 9.3.

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 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 Section 9.1 and Section 9.3.

12.7.5. ALLERGIC REACTION

Grade 1 allergic reaction (Pruitis 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 Section 9.1 and Section 9.3.

Grade 2 allergic reaction (Localized urticaria):

Subjects with Grade 2 allergic reaction should be evaluated by the Investigator immediately. The study drug will 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 9.1 and Section 9.3.

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 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

12.7.6. 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: Palatability Questionnaire

The following questionnaire will be administered to each subject within 10 minutes following any dose of the DTG where it is given as a dispersion. Subjects will be given the questionnaire to read prior to receiving this dose.

Subject #: _____ Date: _____ Treatment:_____

Page 1 of 4

1. Please briefly describe the taste of the product in your own words (one word, short phrase descriptions are acceptable).

2. Please rate the palatability (acceptability of taste) of the product by checking a rating below.

____1 = unacceptable (would not use product under any circumstances)
____2 = neutral/acceptable
____3 = very good

3. Please check **all** the descriptors that apply to the product.

_____ Sweet

_____ Sour/tart

_____ Bitter

_____ Fruity

_____ Nutty

_____ Chalky

_____ Medicinal

4. Please select the descriptor you most closely associate with the flavor of the product (i.e., select one).

_____ Sweet

_____ Sour/tart

_____ Bitter

_____ Fruity

_____ Nutty

_____ Chalky

_____ Medicinal

_____ Other (please specify)_____

Subject #: _____ Date: _____ Treatment:_____

5. Please rate the mouth feel of the product by checking a rating below.

_____ 1= unacceptable (would not use product under any circumstances)
_____ 2= neutral/acceptable
_____ 3= very good

6. Please rate the aroma of the product by checking a rating below.

____1 = unpleasant/unacceptable aroma
____2 = neutral/acceptable aroma
____3 = pleasant/desirable aroma

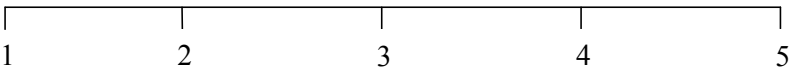
7. Please rate the product aftertaste by checking a rating below.

____1 = unpleasant/unacceptable (e.g. need/desire to wash taste out of mouth)
____2 = neutral/acceptable
____3 = pleasant/desirable

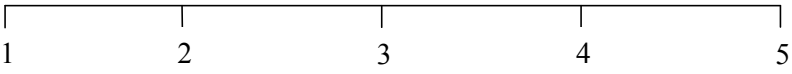
Subject #: _____ Date: _____ Treatment:_____

8. For each of the following attributes please circle the number that best describes your perception of each attribute.

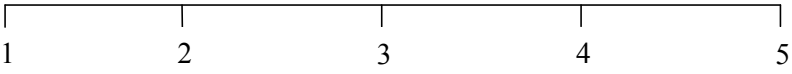
g. Flavor intensity Mild Average Strong



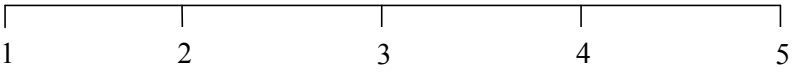
h. Aroma Mild Average Strong



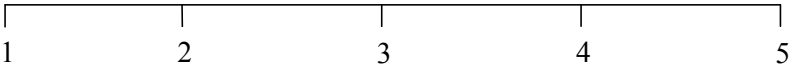
i. Sweetness Not Sweet Sweet Very Sweet



j. Sour/tartness Mild Average Strong



k. Consistency Thin Average Thick



Subject #: _____ Date: _____ Treatment:_____
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9. Based on your response to #8, please circle the number on a scale of 1 to 5 that best describes your recommendation for modifying this product where:

   1 = Reduce as much as possible
   3 = Leave as is
   5 = Increase as much as possible

l. Flavor intensity **Reduce** **Leave as is** **Increase**

1 2 3 4 5

m. Aroma

1 2 3 4 5

n. Sweetness

1 2 3 4 5

o. Sour/tartness

1 2 3 4 5

p. Consistency

1 2 3 4 5

10. Please rate the color of the product on a scale of 1 to 3, where:

____1 = unpleasant
____2 = neutral/acceptable
____3 = pleasant/desirable

11. Do you have any other suggestions for changing/improving the flavor of this product?