TITLE PAGE

Protocol Title: A Phase I, Open-label, Single-dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Dolutegravir + Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy participants of Japanese descent

Protocol Number: 212312

Compound Number: GSK3365791

Study Phase: Phase 1

Short Title: Study to Evaluate Pharmacokinetics, Safety and Tolerability of Dolutegravir and Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy participants of Japanese descent

US IND Sponsor Name and Legal Registered Address:

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In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy.

This study is sponsored by ViiV Healthcare. Parexel with GlaxoSmithKline are supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information: Can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND Number 123306

Approval Date: 04-APR-2019

SPONSOR SIGNATORY:

PPD

April 4, 2019

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I, Open-label, Single-dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Dolutegravir + Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy participants of Japanese descent

Short Title: Study to Evaluate Pharmacokinetics, Safety and Tolerability of Dolutegravir + Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy participants of Japanese descent

Rationale:

Dolutegravir (DTG), a human immunodeficiency virus (HIV)-1 integrase inhibitor (INI), and rilpivirine (RPV), a non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI), are each approved in the United States (US), European Union, and other countries for the treatment of HIV-1 infection, in combination with other antiretrovirals (ARVs). JULUCA is a fixed-dose single tablet containing dolutegravir and rilpivirine approved by the US Food and Drug Administration in 2017 and the European Commission and Japan Ministry of Health Labor & Welfare (MHLW) in 2018. JULUCA is a complete regimen indicated for the treatment of HIV-1 infection in ARV-experienced adult patients who are switching from their current ARV regimen to the 2-drug regimen while their viral load is suppressed to <50 copies/milliliter (c/mL).

Although, the pharmacokinetics (PK), safety and tolerability of DTG/RPV (50 mg/25mg) fixed-dose combination (FDC) tablets have been extensively studied in participants not of Japanese heritage, these parameters have not been assessed exclusively in Japanese participants. To support a post-approval commitment for DTG/RPV 50 mg/25 mg FDC in Japan, this study will characterize the PK, safety and tolerability of a single dose DTG/RPV 50 mg/25 mg FDC in a healthy adult Japanese population. This study will be conducted under fed conditions to maintain alignment with the JULUCA product label.

Objectives and Endpoints:

Objectives	Endpoints
Primary To evaluate the PK of DTG and RPV following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese participants.	Plasma DTG and RPV $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, C_t, and C_{24} following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy adult Japanese participants.
Secondary To evaluate the safety and tolerability of DTG/RPV FDC in healthy, adult Japanese participants.	Safety and tolerability parameters, adverse event (AE)/serious adverse events (SAE), observed and change from baseline clinical laboratory values, and vital sign assessments.

$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point
$AUC_{(0-\infty)}$ = area under the plasma concentration time curve from time zero to infinity
$AUC_{(0-24)}$ = area under the plasma concentration time curve from time zero to 24 hours
$AUC_{(0-72)}$ = area under the plasma concentration time curve from time zero to 72 hours
$\%AUC_{ex}$=% of $AUC_{(0-\infty)}$ that was extrapolated
C_{max} = maximum observed concentration
C_{24} = concentration at 24h post-dose
Ct = last quantifiable concentration
t = time of last quantifiable concentration
t_{lag} = absorption lag time
t_{max} = time of maximum observed concentration
λz=apparent elimination rate constant
$t_{1/2}$ = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

Overall Design:

This will be a single-center, single dose, open-label study in adult Japanese healthy participants to evaluate the PK, safety and tolerability of the DTG/RPV 50 mg/25mg FDC tablet. The study will consist of screening, treatment and follow-up phases. Participants will have a screening visit within 28 days prior to receiving the study intervention. Enrolled participants will receive a single oral dose of the DTG/RPV 50 mg/25 mg FDC tablet in a fed state. Safety assessments including, clinical laboratory safety tests and adverse event reports will be performed throughout the study. Serial PK samples will be collected pre-dose through 264 hours post-dose. All participants will have a follow-up visit within 12-17 days after the last dose of study intervention.

Disclosure Statement: This is a single group, single arm study that has no masking.

Number of Participants:

A maximum of 16 healthy adult Japanese subjects will be enrolled such that a minimum of approximately 13 evaluable subjects complete the study with at least 3 participants of each gender enrolled.

Intervention Groups and Duration:

Each subject will have a screening visit within 28 days prior to the one treatment period with a single dose of study drug and a follow-up visit up within 12-17 days after the single dose of study intervention. The total duration of participation of a subject in this study will be approximately 45 days.

Data Monitoring Committee: No

1.2. Schedule of Activities (SoA)

Table 1 Screening Visit

Procedure	Screening (up to 28 days before Day 1)
Informed Consent	X
Inclusion and exclusion criteria	X
Demographics	X
Brief physical examination including height, weight and body mass index (BMI)[1]	X
Medical history including substance (Drug, Alcohol, Tobacco and Caffeine) usage	X
Urine drug / serum alcohol / Cotinine screening	X
Triplicate 12-Lead Electrocardiogram (ECG)[4]	X
Vital Sign (VS) measurements[4]	X
Serum or urine pregnancy test (WOCBP only)	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
HIV, Hep B and Hep C Screening[2]	X
Clinical laboratory assessments (hematology, chemistry, urinalysis, including liver chemistries)[3,4]	X

[1] A brief physical examination will include at a minimum, assessments of the skin, cardiovascular, and respiratory.
[2] If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
[3] Glucose non-fasting at screening.
[4] VS, Clinical laboratory assessments, ECG can be repeated once.

Table 2 Study Intervention Period Assessments

Procedure	Day -1	Study Intervention Period										Follow-Up (12 -17 days post last dose) [2,3]	Notes
		Day											
		1			2	3	4	6	8	10	12		
		Pre Dose	0 hr	Post Dose	24 hr	48 hr	~72 hr	~120 hr	~168 hr	~216 hr	~264 hr		
Admission to Unit	X												
Discharge						X							
Outpatient Visit							X	X	X	X	X	X	
Brief Physical Exam[1]	X												
Pregnancy test (urine or serum)	X											X	
Urine/Drug/Alcohol/Cotinine	X												Illicit Drug/Alcohol/Cotinine performed at the standard practice of the site.
12-Lead ECG	X												Single ECGs will be collected
Vital Signs (VS) measurements	X	X										X	Single VS measurements will be performed at all time points.
Safety lab assessments (Hematology,Chemistry)	X					X							Glucose fasting is required approximately 10 hours prior to dosing on Day -1 and at least 6 hours at Day 3 post dose.
DTG/RPV FDC Dosing			X										1. Subjects will fast for ~10 hours and receive the dose ~30 minutes (±5 minutes) after the start of a standardized moderate fat breakfast
Pharmacokinetic Sampling		X		Collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 12, 16, 24, and 48 hours post-dose			X	X	X	X	X		1. Subjects should be scheduled to provide PK samples in the morning on Days 4, 6, 8, 10, and 12; Days 8, 10, and 12 are for RPV sampling only. 2. The 4-hour post-dose sample must be drawn prior to the subjects' first post-dose meal

Procedure	Day -1	Study Intervention Period									Follow-Up (12 -17 days post last dose) [2,3]	Notes
		Day										
		1			2	3	4	6	8	10	12	
		Pre Dose	0 hr	Post Dose	24 hr	48 hr	~72 hr	~120 hr	~168 hr	~216 hr	~264 hr	
Serious Adverse Event (SAE) Review	X	←==========X==========→									X	
Adverse Event (AE) Review		←==========X==========→									X	
Concomitant medication review	X	←==========X==========→									X	

[1] Brief examinations may be made full examinations and laboratory procedures may be repeated, if needed, at the discretion of the investigator.
[2] If withdrawal is after Day 3, but before Follow Up procedure, please perform all Follow Up study procedures.
[3] Follow up study procedures can be performed on Day 12.

- The timing and number of planned study assessments, including safety and PK 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.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment.The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

Dolutegravir (DTG), a human immunodeficiency virus (HIV)-1 integrase inhibitor (INI), and rilpivirine (RPV), a non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI), are each approved in the US, European Union, and other countries for the treatment of HIV-1 infection, in combination with other antiretrovirals (ARVs). JULUCA is a fixed-dose single tablet containing dolutegravir and rilpivirine approved by the US Food and Drug Administration (FDA) in 2017 and the European Commission and Japan Ministry of Health Labor & Welfare (MHLW) in 2018. JULUCA is a complete regimen indicated for the treatment of HIV-1 infection in ARV-experienced adult patients who are switching from their current ARV regimen to the 2-drug regimen while their viral load is suppressed to <50 copies/milliliter (c/mL). For more details, please reference the current JULUCA Prescribing Information [Juluca USPI, 2017].

Although, the pharmacokinetics (PK), safety and tolerability of DTG/RPV 50 mg/25 mg fixed-dose combination (FDC) tablet have been extensively studied in participants not of Japanese heritage, these parameters have not been assessed exclusively in Japanese participants. To support a post-approval commitment for the DTG/RPV 50 mg/25 mg FDC tablet in Japan, this study will characterize the PK, safety and tolerability of a single dose of the DTG/RPV 50 mg/25 mg FDC tablet in a healthy adult Japanese population. This study will be conducted under fed conditions to maintain alignment with the JULUCA Prescribing Information [Juluca USPI, 2017].

2.2. Background

TIVICAY (dolutegravir) was first approved in the United States in 2013 and is currently approved globally in more than 100 countries including, the Japanese Pharmaceuticals and Medical Devices Agency in 2014. DTG is an INI with low to moderate inter-subject PK variability, a predictable exposure-response relationship, and a 14-hour plasma half-life. Although co-administration of DTG with low-, moderate-, and high-fat meals increased DTG exposures (area under the plasma concentration-time curve from time 0 to infinity $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, respectively), the TIVICAY product label states that the approved dose regimen is 50 mg once daily taken with or without food based on efficacy results of Phase 3 trials in treatment-naive or treatment-experienced, INI-naive patients who took DTG without regard to mealtimes [TIVICAY USPI, 2015] . More information on the efficacy, PK, safety and drug interaction potential of DTG based on an extensive program of Phase I to III clinical trials can be found in the Investigator Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/09].

EDURANT (rilpivirine), an NNRTI with *in vitro* activity against wild type virus and a broad range of NNRTI-resistant viruses, is approved in multiple countries including the US, Europe, Canada and Japan for the treatment of antiretroviral drug- naive patients (with viral load ≤100,000 c/mL) at a dose of 25 mg once daily. RPV is primarily metabolized by CYP450 3A and has a half-life of approximately 50 h. The long half-life of RPV requires a lengthy PK sampling period of RPV to adequately characterize the terminal elimination phase and ensure that PK parameters are well-estimated. More

detailed information about efficacy, safety, and clinical pharmacology from an extensive program of Phase I-III clinical trials can be found in the RPV Investigator's Brochure [Janssen EDMS Number EDMS-ERI-3713711, 15.0., 2018].

JULUCA (dolutegravir and rilpivirine) is a fixed-dose single tablet containing a two-drug combination of dolutegravir and rilpivirine. JULUCA is indicated for the treatment of HIV-1 infection in ARV-experienced adult patients who are switching from their current ARV regimen to the 2-drug regimen while their viral load is suppressed to <50 copies/milliliter (c/mL). For more details, please reference the current JULUCA Prescribing Information [Juluca USPI, 2017].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, and summaries of findings from both clinical and non-clinical studies conducted with DTG and RPV may be found in the product label for JULUCA [Juluca USPI, 2017], and the Investigator's Brochure and product labels for DTG [GlaxoSmithKline Document Number RM2007/00683/09] [TIVICAY, 2015] and RPV [Janssen EDMS Number EDMS-ERI-3713711, 12.0.] [EDURANT, 2015]. The following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and RPV] [GSK3365791**]** **Refer to IBs for additional information**		
DTG - Hypersensitivity reaction (HSR) and rash **RPV - Rash**	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported. **RPV:** Rash is a recognized risk for the NNRTI class; however, the severe rash defined above that are labelled for efavirenz and nevirapine were not seen with RPV in clinical trials. In Phase III clinical trials, skin events of interest were reported at a lower incidence and grades, and resulted in fewer subject withdrawals, in the RPV group than in the efavirenz group and were mostly driven by the individual preferred term Rash.	*Since this is a single dose study, discontinuation of study intervention for suspected HSR and rash will not be applicable for participants.* *Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2).* *In the event of a HSR, participants should be evaluated by the Investigator immediately. 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. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the adverse event and standard management should be undertaken.* *The subject informed consent form includes information on this risk and the actions subjects should take in the event of: 1) an HSR or associated signs and symptoms; or 2) developing any type of rash or skin abnormality.* *The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings).* *If the etiology of the rash can be definitively diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
		the diagnosis provided.
DTG and RPV - Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for 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. **RPV:** Hepatic events have been reported in patients receiving a RPV containing regimen. Patients with underlying HBV or HCV, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of RPV. A few cases of hepatic toxicity have been reported in patients receiving a RPV containing regimen who had no pre-existing hepatic disease or other identifiable risk factors.	*Subjects meeting either of the following criteria during the screening period are excluded (Section 5.2).* • *A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result at screening.* • *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 >1.5xULN.* *Since this is a single dose study, discontinuation of study intervention for suspected DILI and if the liver chemistry stopping criteria are met will not be applicable for participants.*
DTG - Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	*Increases in serum creatinine are not expected to have any adverse effect and; therefore, do not require mitigation for this protocol.* *Subjects with Creatinine clearance (CrCL) <60 mL/min will be excluded from the study.*
RPV - Corrected QT interval (QTc) prolongation	In healthy subjects, supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (ECG). RPV at the recommended dose of 25 mg administered once daily is not associated with a clinically relevant effect on QTc.	*Screening ECG to identify those with pre-existing prolonged QT interval.*

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 gradings 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.

Benefit Assessment

This is a study in healthy participants, as such there is no expected benefit to administration of DTG/RPV 50 mg/25 mg FDC tablets. There may be benefit to individual participants from the medical evaluations and assessments that could identify conditions that the participant was previously unaware of.

2.3.2. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, please refer to the current JULUCA label [Juluca USPI, 2017] for the potential risks identified in association with the DTG/RPV 50 mg/25 mg FDC tablet.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary To evaluate the PK of DTG and RPV following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese participants.	Plasma DTG and RPV $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, C_t, and C_{24} following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy adult Japanese participants.
Secondary To evaluate the safety and tolerability of DTG/RPV FDC in healthy, adult Japanese participants.	Safety and tolerability parameters, adverse event (AE) /serious adverse events (SAE), observed and change from baseline clinical laboratory values, and vital sign assessments.

$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point
$AUC_{(0-\infty)}$ = area under the plasma concentration time curve from time zero to infinity
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Ct = last quantifiable concentration
t = time of last quantifiable concentration
t_{lag} = absorption lag time
t_{max} = time of maximum observed concentration
λz=apparent elimination rate constant
$t_{1/2}$ = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

4. STUDY DESIGN

4.1. Overall Design

This will be a single dose, open-label study in adult Japanese healthy participants to evaluate the PK, safety and tolerability of DTG/RPV 50 mg/25 mg FDC tablets. The study will consist of screening, treatment and follow-up phases. Participants will have a screening visit within 28 days prior to receiving the treatment. Enrolled participants will receive the DTG/RPV 50 mg/25 mg FDC tablet as a single oral dose in a fed state. Safety assessments including, clinical laboratory safety tests and adverse event reports will be performed throughout the study. Serial PK samples will be collected pre-dose through approximately 264 hours post-dose. All participants will have a follow-up visit within 12-17 days after the last dose of study intervention.

4.2. Scientific Rationale for Study Design

Prior population PK analyses have shown that the PK of DTG and RPV are similar in healthy and HIV-infected participants and race/ethnicity was not identified as a clinically relevant covariate to affect DTG and RPV PK. Therefore, the PK of the DTG/RPV 50 mg/25 mg FDC tablet is expected to be similar in Japanese healthy subjects and HIV-infected Japanese patients and the result from this study in healthy Japanese subjects can be applied to HIV-infected Japanese patients.

4.3. Justification for Dose

JULUCA, a two-drug regimen of DTG/RPV, is indicated as a complete regimen for the treatment of HIV-1 in adults who are virologically suppressed. The approved adult dose of JULUCA (DTG/RPV) is 50 mg/25 mg taken orally once daily with a meal. Since race/ethnicity was not identified as a significant covariate to affect DTG and RPV PK in prior population PK analyses, no differences in PK are expected with the approved 50 mg/25 mg FDC tablet to be administered to healthy, Japanese adults in this study. In addition, both products as single agents and as JULUCA, and as part of other fixed dose combinations are approved at the same dosages in Japan.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial globally.

5. STUDY POPULATION

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

The adherence to the study design requirements, including those specified in the SoA, are essential and required for study conduct.

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 respective IBs and/or product labels.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics:

2. Participants who were born in Japan with 4 ethnic Japanese grandparents. Participants who have not lived outside Japan for more than 10 years and who are Japanese passport holders (current or expired).
3. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG).

Weight

4. Body weight ≥50 kg (110 lbs) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive).

Sex

5. Male and female

a) Male Participants: No restrictions

b) Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 4. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 .

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data.
2. Abnormal blood pressure [as determined by the investigator]
3. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
4. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. QTcF >460 msec; [Based on the average of the 12 Lead ECG triplicate readings obtained at Screening]

   NOTES:

- The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), and/or another method, 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.

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing, see Section 6.5. Acetaminophen, as listed in Section 6.5, is allowed.

Prior/Concurrent Clinical Study Experience

8. Participation in the study would result in loss of blood or blood products in excess of 500mL within 56 days.

9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
10. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research

Diagnostic assessments

11. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention.
12. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

    NOTE:

    - Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

13. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention

    NOTE:

    - Test is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

14. Positive pre-study drug/alcohol screen.
15. Positive human immunodeficiency virus (HIV) antibody test.
16. Regular use of known drugs of abuse.
17. Creatinine clearance (CrCL) <60 mL/min.

Other Exclusions

18. Employment with Janssen, ViiV, GlaxoSmithKline(GSK), or with the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator.
19. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
20. Regular alcohol consumption within 6 months prior to the study defined as:

    An average weekly intake of > 14 units for males or >7 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

21. Sensitivity to heparin or heparin-induced thrombocytopenia.
22. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Once in the clinical unit subjects will not be allowed to eat anything other than the food provided by the study centre.
- At all times subjects will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pomelos, exotic citrus fruits, quinine, mustard greens and poppy seeds from 7 days prior to the first dose of study medication until after the final PK sample.

- Subjects will fast (except water) from approximately 10 hours prior to dosing and will receive a standardized moderate fat breakfast approximately 30 minutes prior to dosing. Subjects will consume this entire meal steadily over 25 minutes. Dose administration will occur approximately 30 minutes after the start of meal consumption (so as to allow approximately 5 minutes for dose preparation). Subjects will not receive any further food until 4 hours post-dose. Other than the 240 mL of water consumed at dosing, subjects will not be permitted water between 2 hours prior to dosing to 2 hours post dose. The moderate fat meal consists of (approximately 625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat):

  1 English muffin
  1 hard cooked egg
  1 slice (0.5oz) American cheese
  1 sausage link or patty (1 oz)
  1 cup red seedless grapes
  6 fl oz cranberry juice
  8 fl oz skim/nonfat milk.

- At all other times during inpatient treatment, subjects will receive meals as specified by the site standards.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from screening until after the final follow-up visit. As per SOA, a negative cotinine test is required at screening.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Table 3 Study Intervention

Intervention Name	JULUCA (Dolutegravir and Rilpivirine) 50 mg/25 mg FDC tablet
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	Dolutegravir 50 mg, Rilpivirine 25 mg
Dosage Level(s)	Single dose – 50 mg/ 25 mg tablet single dose
Route of Administration	Oral
IMP and NIMP	NIMP
Sourcing	Purchased by the Investigator

6.2. Preparation/Handling/Storage/Accountability

No special preparation of the study intervention is required for this study.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled 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 intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual provided by the site.
- Under normal conditions of handling and administration, study intervention 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single center, single dose study.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention 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 intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Use of H_2-blockers, proton-pump inhibitors, antacids, vitamins, calcium or iron supplements are strictly prohibited within 7 days prior to the first dose of study medication until 12 hours post-dose. In addition to these drugs, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study.

6.6. Dose Modification

As this is a single dose study in healthy participants, there are no planned dose modifications.

6.7. Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

As this is a single dose study, the permanent discontinuation of study intervention for a participant is non-applicable.

7.1.1. Liver Chemistry Follow Up Criteria

Liver chemistry follow up assessments and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Since this is a single dose study, discontinuation of study intervention if the liver chemistry stopping criteria is met will not be applicable for participants. Therefore, increased monitoring criteria indicated in liver safety required actions and follow up assessments, as outlined in Appendix 6, Section 10.6, will be employed.

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

7.1.2. QTc Stopping Criteria

This section is not applicable in this study.

7.1.3. Temporary Discontinuation

This Section is not applicable to this study.

7.2. Participant Discontinuation/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 for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- If withdrawal is after Day 3, but before Follow Up procedure, please perform all Follow Up procedures as per SoA.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.3. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is 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 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 the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
  1. Vital Signs
  2. Blood Draws

  NOTE: The timing of the assessments should allow the blood draw to occur as close as possible to the exact nominal time.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.2.1. Physical Examinations

- A brief physical examination will include, at a minimum, assessments of the skin, respiratory and cardiovascular system.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature, pulse rate, and blood pressure (collected as standard for the site) and will be assessed.
- Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained, in supine or semi-supine position after 5 minutes rest at Day-1 as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Triplicate ECG are required at Screening at which 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which

are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 17 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal (grade 2 or lower) by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Ideation and Behaviour Risk Monitoring

Not applicable.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA. However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. 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 after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- 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 3.
- 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.

8.3.3. 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 of special interest (as defined in Section 2.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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 intervention 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 intervention 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 and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Not applicable for this study.

8.3.6. Cardiovascular and Death Events

Not applicable for a healthy volunteer study

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

Not applicable for this study.

8.3.8. Medical Device Incidents (Including Malfunctions)

Not applicable for this study.

8.4. Treatment of Overdose

For this study, any dose of greater than 1 FDC tablet of DTG 50 mg / RPV 25 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 25 days).
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention 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 CRF.

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

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

- Blood samples for pharmacokinetic analysis of DTG and RPV will be collected at the time points indicated in SoA. The 4-hour post-dose sample must be drawn prior to the subjects' first post-dose meal. The actual date and time of each blood sample collection will be recorded.
- For each DTG PK sample, 2 mL of blood will be collected into di-potassium ethylenediaminetetraacetic acid (K_2EDTA) tubes for DTG quantification and **protected from light**.

- For each RPV PK sample, 2 mL of blood will be collected into sodium heparin tubes for RPV quantification and **protected from light**.

- Processing, storage and shipping procedures are provided in the Study Reference Manual provided by the site or other equivalent document. **Please pay special attention to the light protection procedures for both DTG and RPV collections and processing.**

8.5.1.1. Sample Processing Procedures

- If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, will be kept patent with normal saline, and will be removed after the last blood sample is collected or earlier if the subject requests. To avoid artificial dilution of the PK samples by saline, 1 mL of whole blood will be collected and discarded before each whole blood sample is collected.
- Collect each serial whole blood PK sample as close as possible to the planned time relative to dosing detailed in the protocol. Collect a whole blood (2 mL) sample into a properly labelled K_2EDTA evacuated blood collection tube for DTG and a properly labelled sodium heparin tube for RPV. Record the date and exact time that each sample is collected in the CRF. All samples should be **protected from light** at all times by putting them in closed boxes, wrapping with aluminium foil or handling under yellow light.

8.5.1.2 Sample Storage Conditions

For DTG PK samples, immediately after collection, gently invert (**do not shake**) the blood collection tube 8-10 times to mix the K_2EDTA anti-coagulants with the whole blood and place the samples at room temperature **protected from light**. For RPV PK samples, immediately after collection, gently invert (**do not shake**) the blood collection tube 8-10 times to mix the sodium heparin anti-coagulants with the whole blood and place the samples at room temperature **protected from light**.

- All samples **must be protected from light** at all times by putting them in closed boxes, wrapping with aluminium foil or handling under yellow light.
- Within 45 minutes of sample collection for both DTG and RPV, centrifuge for 10 minutes, at 1500 - 2000 G, in 4°C.
- Within 30 minutes of centrifugation, using a polyethylene pipette, transfer plasma into separate, single, and appropriately labelled 2 mL Amber/Brown Sarstedt tubes.
- Immediately freeze the storage tubes in an upright position at -20°C.

DTG and RPV are photosensitive so all plasma sample manipulation procedures (sample collection and analytical steps) will be performed protecting samples from light. Limit the time between centrifugation and transfer of the plasma to amber/brown tubes as much as possible, with care to close the centrifuge lid between the different actions. If it is not possible to transfer the blood to plasma immediately; the centrifuged tubes should remain protected from light at all times (boxes or foil).

8.5.2. Sample Analysis

Dolutegravir will be extracted from plasma using protein precipitation followed by ultra performance liquid chromatography triple quadrapole mass spectrometry (UPLC-MS/MS) using the previously validated method, Quantitation of GSK1349572 in Human Plasma via UPLC with MS/MS Detection (PPD method number, P1170.02; [GlaxoSmithKline Document Number 2015N231443_00]. The analysis will be performed by PPD, 3230 Deming Way, Middleton, WI, USA. The DTG sample analysis will be under the management of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Raw data will be archived at the bioanalytical site.

Rilpivirine will be extracted from plasma using protein precipitation followed by UPLC-MS/MS using the previously validated method, validation of a method for the determination of JNJ-16150108 (PRA-NL-SML-2159/JJP110EL-181103-C/BA13223). The potential conversion of rilpivirine to the Z-isomer will be evaluated as part of the rilpivirine sample analysis. The analyses will be performed by PRAHS, Amerikaweg 18, 9407 TK Assen, The Netherlands. The RPV sample analysis will be under the management of Janssen. Raw data will be archived at the bioanalytical site.

Dolutegravir and rilpivirine sample analyses will be performed under light protection procedures.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study will seek to characterize the pharmacokinetics of DTG and RPV following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese subjects. Also, this study will seek to assess the safety and tolerability of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese participants. No formal statistical hypothesis will be tested.

9.2. Sample Size Determination

Approximately 16 participants will be enrolled and assigned to study intervention such that 13 evaluable participants complete the study.

There was no formal calculation of power or sample size for this study.

9.2.1. Sample Size Assumptions

Based on the previous DTG and RPV BE study (Study 201676) [GlaxoSmithKline Document Number 2015N243078_01], the intersubject coefficients of variation (CVs) for AUC0-t, AUC0-inf and Cmax of a single dose of DTG+RPV (given as either single components or a fixed dose combination formulation) in a fed state were estimated to be less than or equal to 43.66% in healthy non-Japanese adult subjects. Using a conservative estimate of 43.66% for intersubject CV and a sample size of 13 subjects, the true mean AUC0-t, AUC0-inf and Cmax of DTG+RPV FDC were estimated to be within 80% to 125% of the observed geometric means with 95% confidence.

9.2.2. Sample Size Sensitivity

Not applicable.

9.3. Populations for Analyses

All of the data that is databased will be presented in subject listings and where appropriate presented in summary tables.
For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
Safety	All participants who enrolled in the study and received at least one dose of study drug.
Pharmacokinetic (PK)	All participants in the Safety population for whom a PK sample was obtained and had evaluable PK assay results.

9.4. Statistical Analyses

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

Data will be listed and summarized according to GlaxoSmithKline reporting standards where applicable.
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.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1. Efficacy Analyses

Not Applicable.

9.4.2. 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. All safety data will be listed.

Full details will be provided in the Reporting and Analysis Plan.

All safety analyses will be performed on the Safety Population.

9.4.3. Pharmacokinetic Analysis

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling & Simulation department within GlaxoSmithKline, or its designee.

Plasma DTG and RPV concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin version 6.3 or higher. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, please refer Objectives and Endpoints (Section 3), for the pharmacokinetic parameters that will be determined, as data permit.

Pharmacokinetic data will be listed and may be presented in graphical form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline.

Full PK analyses will be described in the reporting and analysis plan.

9.4.4. Data Monitoring Committee (DMC)

Not applicable for this study.

9.5. Interim Analysis

Not applicable for this study

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., 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

10.1.2. 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.

10.1.3. 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.

10.1.4. 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.

10.1.5. Committees Structure

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 multicenter 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.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. 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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.

10.1.8. 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 CRF 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 Study Reference Manual.

10.1.9. 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 intervention development

10.1.10. 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 multicenter 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the timepoints indicated in the SoA.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
- Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose[2]	Calcium	Alkaline phosphatase	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• FSH (as needed in women of probable non-child bearing potential only) • Creatinine Clearance • [Serum or urine] [alcohol, cotinine, and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3] • HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody

NOTES :

1. Details of liver chemistry criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).
2. As noted in the SoA, Glucose fasting is required approximately 10 hours prior to dosing on Day -1 and at least 6 hours at Day 3 post dose. At all other timepoints, glucose will be non-fasting (i.e, at Screening).
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event (AE)

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 intervention 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 intervention 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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 (e.g., 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.

10.3.2. Definition of Serious Adverse Event (SAE)

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

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

- Results in death
- 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.

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.

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.
Is a congenital anomaly/birth defect
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.

10.3.3. Recording and Follow-Up of 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 CRF. • 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 CRF 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 sufficient 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.

IMPORTANT – PLEASE NOTE THE FOLLOWING STATEMENT:
For this study the above criteria regarding mild, moderate and severe will be used in combination with the Division of AIDS (DAIDS) Table for Grading Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017 (Appendix 9).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention 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 intervention 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. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

10.3.4. Reporting of SAE to GSK

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, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- 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 Study Reference Manual.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Reference Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
   - Females on HRT and whose menopausal status is in doubt will be excluded from the study.

10.4.2. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating

in this study. This applies only to male participants who receive the study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) 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 intervention by the investigator, will be reported to GSK as described in Appendix 3. 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 participant who becomes pregnant while participating

- will be withdrawn from the study.

10.5. Appendix 5: Genetics

Not Applicable

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry follow up criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). In this study, this guidance is for following any subject who has these elevated values post-dosing.

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

Phase I liver chemistry criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Follow Up Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to</td><td>• Viral hepatitis serology[3]
• Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend
• 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,</td></tr>
</table>

Liver Chemistry Follow Up Criteria	
within baseline • A specialist or hepatology consultation is recommended	other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention 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, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody or Hepatitis E RNA

10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not Applicable

10.8. Appendix 8: Country-specific requirements

Not Applicable

10.9. Appendix 9: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for AE reporting. A grading (severity) scale is provided for each AE term. Please refer to the DAIDS grading table Version 2.1, July 2017 (https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf) for more information.

10.10. Appendix 10: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALT (SGPT)	Alanine Aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)
ART	Antiretroviral Treatment
ARV	Antiretroviral
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours
AUC_{0-t}	Area under the concentration-time curve from time 0 to the last measurable timepoint
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
BMI	Body mass index
BP	Blood Pressure
BUN	Blood urea nitrogen
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences
Ct	Last quantifiable drug concentration
CI	Confidence interval
CL/F	Apparent oral clearance
C_{max}	Maximal drug concentration
CNS	Central nervous system
C_{24}	Drug concentration at 24 hours post-dose
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CRF	Case report form
CrCl	Creatinine Clearance
CSR	Clinical Study Report
C_t	Last quantifiable concentration
CVw%	Coefficients of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug Induced Liver Injury
dL	Decilitre
DMC	Data Monitoring Committee
DTG	Dolutegravir
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	Fixed Dose Combination

FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
h	Hours
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C Virus
HIPPA	Health Insurance Portability and Accountability Act
HIV-1	Human Immunodeficiency Virus type 1
HPLC	High-performance liquid chromatography
HR	Heart Rate
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
IND	Investigational New Drug
INI	Integrase inhibitor
INR	International Normalized Ratio
IP	Investigational Product
IU	International Units
IRB	Institutional Review Board
K_2EDTA	Di-potassium ethylenediaminetetraacetic acid
Kg	Kilograms
Lbs	Pounds
LDH	Lactate Dehydrogenase
m	Meters
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	Milligrams
MHLW	European Commission and Japan Ministry of Health Labor & Welfare
mL	Millilitre
MSDS	Material Safety Data Sheet
NRTI	Nucleoside reverse transcriptase inhibitor
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate according to Fridericia's formula

RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic Acid
RPV	Rilpivirine
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SJS	Stevens-Johnson syndrome
SUSAR	Suspected unexpected serious adverse reactions
t	Time of last quantifiable concentration
$t_{1/2}$	Half-life
t_{lag}	Absorption lag time
t_{max}	Time to observed maximal drug concentration
TEN	Toxic epidermal necrolysis
µg	Microgram
ULN	Upper Limit of Normal
UPLC-MS/MS	Ultra performance liquid chromatography triple quadrapole mass spectrometry
US	United States
USPI	United States Prescribing Information
VS	Vital Signs
Vz/F	Apparent oral volume of distribution
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

Trademark Information

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DAIDS
EDURANT
Phoenix WinNonlin
SAS

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