Protocol Amendment 05

Study ID: 205858

Official Title of Study: Open-label access to dolutegravir for HIV-1 infected children and adolescents completing IMPAACT Studies P1093 and P2019.

NCT number: NCT03016533

Date of Document: 21-Jun-2022

TITLE PAGE

Protocol Title:	Open-label access to dolutegravir for HIV-1 infected children and adolescents completing IMPAACT Studies P1093 and P2019.

Protocol Number: 205858 / Amendment 05
Compound Numbers: GSK1349572 and GSK2619619

Study Phase: 3B
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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 VP, Global Medical Strategy.

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

Regulatory Agency Identifying Number(s): Tivicay US IND# 075382; Triumeq US IND# 114820; EudraCT# 2011-001646-16

Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

Sponsor Signatory:
Sherene Shakib Min, MD, MPH
Vice President, Head of Clinical Development,
ViiV Healthcare
Approval Date: 06 Jun 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 05	06 Jun 2022	TMF-14008177
Amendment 04	10-December-2020	2016N282439_04
Amendment 03	27-June-2019	2016N282439_03
Amendment 02	29-June-2018	2016N282439_02
Amendment 01	26-September-2016	2016N282439_01
Original Protocol	23-August-2016	2016N282439_00

Amendment 05 – 06 Jun 2022

Overall Rationale for the Amendment:

Below mentioned are the changes with rationale incorporated in Amendment 05:

Exclusion criteria were clarified to more closely align with the penultimate and end of study visit period and assessments in the parent studies.

Device deficiency reporting requirements were removed as the study is outside the scope of United States Food and Drug Administration (US FDA) 21 CFR 4 Subpart B (Regulation of Combination Products).

The DTG 50 mg film coated tablet was approved for use in children weighing 20 kg and above in the Unites States, European Union and many other countries. Therefore, the DTG film coated tablet weight based dosing table in the appendix was removed and replaced with updated dosing instructions for participants weighing 20 kg and above. DTG dispersible tablets may be utilized in patients weighing 3 kg and above.

In addition, the ABC/DTG/3TC (600 mg/50 mg/ 300 mg) immediate release tablet received approval for use in the United States for patients weighing 25 kg and above in March 2022, and ABC/DTG/3TC (60 mg/5 mg/30 mg) dispersible tablet weight-based dosing was approved for use in patients weighing at least 10 kg in the United States at the same time. Additional marketing applications for the ABC/DTG/3TC dispersible tablet and immediate release tablets for pediatric patients are under review by the EMA.

Other changes include minor updates to protocol text with regards to latest template and additions made throughout for protocol text clarity.

Section # and Name	**Description of Change**	**Brief Rationale**
2. Introduction	Added European Medicines Agency (EMA) regulatory approval details.	Updated as per available details.
4.6.1 Risk	Updated footnote associated with	Footnote updated to provide

Section # and Name	Description of Change	Brief Rationale
Assessment for DTG	monitoring SAEs and AEs leading to treatment discontinuation.	clarity.
5.2. Exclusion Criteria (Exclusion Criterion 3) 4.6.2 Risk Assessment for ABC/DTG/3TC	Before: Known ≥Grade 3 laboratory toxicities within 30 days prior to study entry (e.g. neutrophil count, hemoglobin, platelets, aspartate aminotransferase (AST), ALT, lipase, serum creatinine and total bilirubin). Repeat testing is allowed for eligibility determination. NOTE: ≥Grade 3 total bilirubin is allowable, if the subject is on ATV. NOTE: Subjects with laboratory abnormalities considered unrelated to IP may be allowed to enter the study. Thus, if the laboratory abnormality persists upon repeat testing, the subject may be considered for study entry after consultation and approval of the study team. Modified (in bold): Known ≥Grade 3 laboratory toxicities (e.g. neutrophil count, hemoglobin, platelets, aspartate aminotransferase (AST), ALT, lipase, serum creatinine, eGFR and total bilirubin) **would be considered exclusionary if identified at or after the penultimate parent study visit, prior to enrollment in the study.** Repeat testing is allowed for eligibility determination. NOTE: ≥Grade 3 total bilirubin is allowable, if the subject is on ATV. NOTE: Subjects with laboratory abnormalities considered unrelated to IP may be allowed to enter the study. Thus, if the laboratory abnormality persists upon repeat testing, the subject may be considered for study entry after consultation and approval of the study team. **An exception to this note is for participants with confirmed creatinine clearance of less than 30 mL/min in**	Timeframe clarified to more closely align with the penultimate and end of study visit period in the parent studies. Language was amended to maintain uniformity in protocol text of Section 4.6.2 as per updates made to Exclusion criteria 3.

Section # and Name	Description of Change	Brief Rationale
	which DTG/ABC/3TC FDC should not be used.	
5.2 Exclusion Criteria (Exclusion Criteria 5)	Before: ALT ≥5 times the ULN, OR ALT ≥3xULN AND bilirubin ≥1.5x ULN (with >35% direct bilirubin) within 30 days prior to study entry. Subjects with moderate to severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification should be excluded. Modified (in bold): Known ALT ≥5xULN, OR ALT ≥3xULN AND bilirubin ≥1.5x ULN (with >35% direct bilirubin) **would be considered exclusionary if identified at or after the penultimate parent study visit, prior to enrollment** in the study. Subjects with moderate to severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification should be excluded.	Timeframe clarified to more closely align with the penultimate and end of study visit period in the parent studies.
5.2 Exclusion Criteria (Exclusion Criteria 6)	Before: Subjects positive for hepatitis B virus in the parent study (hepatitis B virus surface antigen positive). After (in bold): Subjects positive for hepatitis B virus **at any time prior to entry** (hepatitis B virus surface antigen positive).	Addition made for clarity with respect to parent study timeframe.
5.2 Exclusion Criteria (Previous Exclusion Criteria 6)	Deleted exclusion criteria 6	The eGFR value of <60 is equivalent to DAIDS severity 3 grading. As exclusion criteria 3 rules out laboratory toxicities of grade ≥3, the previous eGFR exclusion criteria was removed and eGFR was added to the list of examples noted within exclusion criteria 3. A reminder was included within exclusion criteria 3 to note that ABC/DTG/3TC should not be

Section # and Name	Description of Change	Brief Rationale
		used in subjects with creatinine clearance of less than 30 mL/min.
6.9 Treatment after the End of the Study	Provisions under which study drug will be made available to subjects has been incorporated.	The duration of subject participation in the study will extend until age appropriate formulations of DTG or ABC/DTG/3TC receive local (by country) regulatory approval and are available commercially in those countries or other availability occurs from another source (e.g. government programs, aid programs, assistance programs, etc.).
Table 7.1.1 Parent Studies: Penultimate Visit Assessments	Addition made to P1093 laboratory evaluations assessment section for "Additional evaluations if clinically indicated"	Updated to align with current P1093 protocol
7.2 Time and Events Table	Updated Table 2 for SAEs during screening visit. Footnote 5 was amended for clarifying SAEs related to study participation will be captured in e-CRF and rest of other SAEs if occurring will be captured in DAIDs sponsored parent studies.	Updated for Clarity and to align with current protocol
7.3 Screening Visit	Addition made with respect to the activities to be conducted during screening visit. Note was amended to mention HIV-1 RNA and pregnancy test results will be recorded in eCRF and source notes respectively.	Details added for maintaining uniformity as per time and events table. Amended for providing distinction for recording requirements and location for HIV-1 RNA and pregnancy tests results.
6.1.1 Medical Devices 7.6.1.5 Medical Device Deficiencies	Removed description of medical device deficiencies reporting activities.	Where required, medical devices are locally sourced by study sites and not supplied by the sponsor in this study. It was therefore determined that

Section # and Name	Description of Change	Brief Rationale
7.6.1.6 Time Period for Detecting Medical Device Deficiencies 7.6.1.7 Prompt reporting of Medical Device Deficiencies to the Sponsor 12.8 Previous Appendix 8 Reporting a Medical Device Deficiency		this study is outside of the scope of the United States Food and Drug Administration (US FDA) 21 CFR 4 Subpart B (Regulation of Combination Products). Hence, Device Deficiency safety requirements are no longer reported.
12.8.1 COVID-19 Experimental Agents	Added HIV-1 RNA collection requirements	As vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, recommendation was added that HIV-1 RNA collection should occur 2-4 weeks from COVID vaccination.
2. Introduction and 6.5.1. DTG Film-Coated Tablets Section 12.2.1 Tivicay DTG Film Coated Tablets	Deleted text for 25 mg and 10 mg DTG film coated tablet. Added text for DTG 5 mg dispersible tablets for oral suspension. Deleted weight based dosing table from Appendix Section 12.2.1 Tivicay DTG film coated tablet. Added guidance for switching from 30 mg DTG to 50 mg film coated tablet.	The DTG 50 mg film coated tablet is approved for use in children weighing 20 kg and above. Therefore, weight based dosing table for Tivicay DTG film coated tablets has been removed from the appendix. A reminder was added to note that participants weighing 20 kg and above may transition to Tivicay DTG 50 mg film coated tablets.
Section 12.7.2 Definition of SAE	SAE definition	Minor update as per template language was incorporated. SAE definition remains the same.
12.7.5. Reporting of SAEs and AEs leading to discontinuation of IP	Removed the Investigator requirement of marking the 'reviewed' box for confirming event causality in the eCRF page within	Removal of repetitive step as an earlier section already describes that the Investigator

Section # and Name	Description of Change	Brief Rationale
to GSK/ViiV Healthcare/PPD	72 hours of submission.	has to perform this check.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event (SAE) Contact Information:

Role	Name	Day Time Phone Number and Fax	After-hours Phone/Cell/ Pager Number	Site Address
Medical Monitor/ SAE Contact	PPD Safety Hotline	(800) 201-8725, phone (888) 488-9697, fax	(800) 201-8725	PPD 929 North Front Street Wilmington, NC 28401

This study is sponsored by ViiV Healthcare LLC. Pharmaceutical Product Development, LLC (PPD) will implement and manage all aspects of this study. The study is performed in compliance with PPD Standard Operating Procedures for all processes involved, including the archiving of essential documents.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205858

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

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY 205858

Rationale

There is an unmet medical need for novel and potent antiretroviral therapy (ART) for children living with human immunodeficiency virus (HIV) infection, and research continues to assess new compounds in the pediatric population. The purpose of this pediatric study is to provide continued access to age appropriate formulations of dolutegravir (DTG), either as single entity DTG (Tivicay or Tivicay PD) or as a part of the fixed dose combination (FDC) ABC/DTG/3TC (Triumeq or ABC/DTG/3TC dispersible tablets), for eligible subjects who have completed either the P1093, or P2019 parent study.

Eligible subjects will have evidence of virological control at the time of completion of the parent studies and will have tolerated Investigational Product (IP) (single entity DTG [Tivicay or Tivicay PD], ABC/DTG/3TC FDC [Triumeq or ABC/DTG/3TC dispersible tablet]), in the parent studies without significant toxicities.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	• Incidence and severity of serious adverse events (SAEs) and any clinical or laboratory adverse events leading to discontinuation of IP (DTG, or ABC/DTG/3TC FDC).
• To provide access to age appropriate formulations of dolutegravir (DTG), either as single entity DTG or as fixed dose combination (FDC) abacavir/dolutegravir/lamivudine (ABC/DTG/3TC), in an open-label protocol to eligible subjects who have completed the P1093, or P2019 parent studies.	
Secondary	
• To assess any serious adverse events (SAEs) and any clinical or laboratory adverse events that lead to the discontinuation of IP (DTG, or ABC/DTG/3TC FDC).	

Overall Design

This is a non-randomized, open-label, multi-center treatment rollover study.

Single entity DTG in age appropriate formulations will be provided to eligible subjects transitioning from parent study P1093. Sites participating in P1093 and this rollover study are in the following countries: Botswana, Brazil, Kenya, South Africa, Tanzania, Thailand, Uganda, United States and Zimbabwe.

ABC/DTG/3TC in age appropriate formulations will be provided to eligible subjects transitioning from parent study P2019. Sites participating in P2019 and this rollover study are in the following countries: Botswana, South Africa, Thailand and the United States.

Treatment Arms and Duration

This study will have 2 treatment arms. One treatment arm will provide age appropriate formulations of single entity DTG to eligible subjects from the P1093 parent study. The second treatment arm will provide age appropriate formulations of DTG as the fixed dose combination ABC/DTG/3TC to eligible subjects from the P2019 parent study. IP will be provided to each subject in this rollover study until any one or more of the following events occur:

- Until age-appropriate formulations of DTG, or ABC/DTG/3TC are available from some other source (e.g. government programs, aid programs, assistance programs etc.) to a subject; OR
- Until a subject is no longer deriving benefit from treatment; OR
- Until a subject meets a protocol-defined reason for discontinuation; OR
- Until development of DTG, or ABC/DTG/3TC is terminated.

Type and Number of Subjects

The subjects will be eligible patients from parent studies, P1093 and P2019. Based on the design of the parent studies, a maximum of 300 pediatric subjects could enroll in this study.

Analysis

No formal hypothesis testing will be performed. Data will provide only descriptive information on safety and tolerability.

2. INTRODUCTION

Dolutegravir (DTG) is a potent integrase strand transfer inhibitor (INSTI). DTG 50 mg film coated tablets, and DTG 5 mg dispersible tablets for oral suspension (marked as Tivicay PD in the US), are approved in most markets. The bioavailability of film coated tablets and dispersible tablets is not comparable; therefore, they must not be used as direct replacements. For example, the recommended adult dose for film coated tablets is 50 mg versus 30 mg for dispersible tablets. Patients changing between film-coated and dispersible tablets should follow the dosing recommendations that are specific for the formulation.

Abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) is a fixed dose combination regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and DTG. ABC/DTG/3TC immediate release tablets (DTG 50 mg/ABC 600 mg/3TC 300 mg) are marketed as Triumeq.

Both DTG and ABC/DTG/3TC have been developed for the treatment of human immunodeficiency virus type 1 (HIV-1) and are approved for use in adults and adolescents in most markets.

- DTG is currently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for adults and for children aged at least 4 weeks and weighing at least 3 kg; and is approved in other markets for children greater than 6 years of age and at least 15 kg weight. Studies of DTG neonates are ongoing.
- ABC is approved for adults and for children as young as 3 months of age.
- 3TC is approved for adults and for children from birth.
- ABC/DTG/3TC immediate release tablets are approved for use in adults and children weighing at least 40 kg (the EMA approval for pediatric use is limited to children at least 12 years of age).
- The ABC/DTG/3TC immediate release tablet was approved for use in pediatric patients weighing 25 kg and above in the US, and ABC/DTG/3TC dispersible tablet (ABC 60 mg/DTG 5 mg/3TC 30) weight-based dosing was approved for use in patients weighing at least 10 kg in the US. Additional marketing applications for the ABC/DTG/3TC dispersible tablet and immediate release tablets for pediatric patients are under review by the EMA.

The purpose of this open label study is to provide continued access to age appropriate formulations of DTG, either as single entity DTG or as part of fixed dose combination ABC/DTG/3TC, for eligible subjects who previously participated in DAIDS sponsored parent studies P1093, or P2019 and who cannot locally access age appropriate formulations of DTG or ABC/DTG/3TC in the public sector.

- Study P1093 is a Phase 1/2 multi-centre, open-label non-comparative intensive pharmacokinetic, safety, tolerability and antiviral activity study of DTG in combination with optimized background regimens in HIV-1 infected infants, children and adolescents.

- Study P2019 is a Phase 1/2 multi-centre, open-label, non-comparative, intensive pharmacokinetic, safety, tolerability and antiviral activity study of ABC/DTG/3TC dispersible and immediate release tablets in HIV-1-infected children.

Eligible subjects are those who have continued benefit from IP as evidenced by virological control at the time of completion of the parent studies and who will have tolerated Investigational Product (IP) (single entity DTG [Tivicay or Tivicay PD], ABC/DTG/3TC [Triumeq or ABC/DTG/3TC dispersible tablets], in the parent study studies without significant toxicities.

2.1. Study Rationale

Children living with HIV infection require access to potent ARV regimens. The purpose of this study is to provide continued access to IP for eligible subjects who have completed the parent studies and continue to benefit from IP administration as evidenced by virologic control at the time of completion of the parent studies. Subjects will receive their age/weight appropriate dose of IP as defined in the parent study; hence, no PK sampling will be performed.

2.2. Brief Background

DTG as an oral tablet formulation has been approved for the treatment of HIV infection in most countries around the world and is now recommended as a component of first line therapy in global treatment guidelines [DHHSa, 2019; EACS, 2018; WHO, 2018].

In addition to being marketed as the Tivicay single-entity film coated tablet and as Tivicay or Tivicay PD single entity dispersible tablet, DTG is also a component of the fixed-dose combination product Triumeq [DTG/abacavir (ABC)/lamivudine(3TC)].

ABC and 3TC form the backbone of several recommended ART regimens. These medications are available separately in tablet and liquid formulations and have also been co-formulated in fixed dose combination tablets (ABC/3TC).

Previous experience in adults has demonstrated that the exposure to DTG, ABC and 3TC in a fixed dose combination formulation is consistent with each drug administered individually. This information was provided as part of the application for Triumeq. Therefore, the DTG dosing recommendations are not expected to differ when DTG is administered in fixed dose combination.

Parent Study P1093 (ING112578)- Single entity DTG (Tivicay and Tivicay PD)

Pediatric study P1093 (ING112578) is being conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) under sponsorship by the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Study P1093 evaluates the safety, tolerability, PK and antiviral activity of DTG in ART-naïve and ART-experienced children and adolescents in various pediatric subsets defined

by age and type of formulation. Types of formulations included in this study are film coated tablets, pediatric granules and dispersible tablets (DT). The DTG granule formulation is no longer being developed for licensure. The study is closed to further accrual; 181 children enrolled.

Study P1093 generated primary data to serve as the basis of pediatric dosing approvals for children from 4 weeks of age.

The P1093 parent protocol includes a 48-week treatment phase, and a long-term safety follow-up up to 192 weeks. As subjects complete the P1093 study, they may require continued access to IP until age appropriate formulations of the drug become available in their markets. This rollover study will provide this needed access for children who meet entry requirements.

At or after the Week 180 visit (penultimate study visit), subjects who are deriving benefit from IP may screen for the 205858 rollover study. If the subject is eligible, the initial Day 1 Visit in 205858 may overlap with the Week 192 visit for P1093. **Parent Study P2019 (205860)- ABC/DTG/3TC**

The P2019 study includes a 48-week treatment phase, with primary visits at Weeks 1, 4, 12, 24, 36 and 48 weeks. At or after the Week 36 visit (penultimate visit in the treatment phase), subjects who are deriving benefit from IP may screen for the 205858 rollover study. If the subject is eligible, the initial Day 1 Visit in 205858 may overlap with the Week 48 visit for P2019. Eligible subjects who complete the Week 48 visit before the rollover study is open to P2019 enrolment, may remain in the P2019 study for up to an additional 96 weeks until the rollover study is available.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	• Incidence and severity of serious adverse events (SAEs) and any clinical or laboratory adverse events leading to discontinuation of IP (DTG, or ABC/DTG/3TC FDC).
• To provide access to age appropriate formulations of dolutegravir (DTG), either as single entity DTG or as fixed dose combination (FDC) abacavir/dolutegravir/lamivudine (ABC/DTG/3TC), in an open-label protocol to eligible subjects who have completed the P1093, or P2019 parent studies.	
Secondary	
• To assess any serious adverse events (SAEs) and any clinical or laboratory adverse events that lead to the discontinuation of IP (DTG, or ABC/DTG/3TC FDC).	

4. STUDY DESIGN

4.1. Overall Design

This is a non-randomized, open-label, multi-center rollover study with two treatment arms. The purpose of this study is to provide continued access to IP for eligible subjects who have completed DAIDS sponsored parent studies P1093 or P2019.

Continued access to DTG will be provided as follows:

- Arm 1: Subjects from the P1093 parent study will continue to receive single entity DTG (Tivicay or Tivicay PD).
- Arm 2: Subjects from the P2019 parent study will continue to receive ABC/DTG/3TC (Triumeq or ABC/DTG/3TC dispersible tablets).

The duration of subject participation in the study will extend until age appropriate formulations of DTG or ABC/DTG/3TC receive local (by country) regulatory approval and are available commercially in those countries or other availability occurs from another source (e.g. government programs, aid programs, assistance programs, etc.).

Patients may be enrolled after all screening procedures have been completed and eligibility reviewed and documented in the patient's medical records. In most cases, the Screening visit will overlap with the subject's penultimate visit on the parent study (at or after Week 180 of P1093, or at or after Week 36 of the P2019 study). Patients who are eligible may enroll and will be seen in the clinic every 12 weeks for a safety evaluation and to receive IP. IP is provided by ViiV Healthcare. Only DTG and ABC/DTG/3TC will be made available through this rollover protocol. Provision of other ARVs as part of

the background regimen are not considered IP and will not be supplied. It is the responsibility of the investigator to source the ARVs of the background regimen locally.

4.2. Treatment Arms and Duration

IP will be provided to each subject on this rollover study until any one or more of the following events occur:

- Until age-appropriate formulations of DTG or ABC/DTG/3TC are available from some other source (e.g. government programs, aid programs, assistance programs etc.) for a subject; OR
- Until a subject is no longer deriving benefit from treatment; OR
- Until a subject meets a protocol-defined reason for discontinuation (See Section 5.3)
- Until development of DTG or ABC/DTG/3TC is terminated.

Once subjects enter this rollover study, they will be seen in clinic every 12 weeks for safety visits until one of the above criteria are filled. Site investigators will monitor safety, and collect and report SAEs, pregnancy reports and any AE that leads to the discontinuation of IP to PPD, the contract research organization charged with conducting the study. SAEs, pregnancies, and events leading to discontinuation of IP (including liver stopping criteria) will be collected and reported to PPD within 24 hours of the investigator becoming aware of the event.

Procedures other than those required to confirm study eligibility and assessment of study endpoints, will be performed as per local standard of care (SoC) (including laboratory evaluations).

4.2.1. DTG for subjects transitioning from P1093

This rollover study will utilize 2 formulations of DTG for subjects transitioning from the P1093 study. DTG film coated tablets and dispersible tablets will be provided to subjects by age and weight bands. Specific weight-based dosing instructions can be found in the current dosing tables in Section 12.2 (Appendix 2).

4.2.2. ABC/DTG/3TC for subjects transitioning from P2019

Two formulations of ABC/DTG/3TC will be utilized for subjects transitioning from the P2019 study. Immediate release tablets and dispersible tablets will be provided to subjects by weight bands.

ABC/DTG/3TC tablets (60 mg/5 mg/30 mg dispersible tablets or 600 mg/50 mg/300 mg immediate release [Triumeq] tablets) will be provided to subjects by age and weight bands. Specific weight -based ABC/DTG/3TC dosing instructions for subjects transitioning from P2019 can be found in the current dosing table in Section 12.2 (Appendix 2).

In addition to the triple-agent fixed dose combination formulations noted above, ViiV Healthcare Ltd will provide DTG 5mg DT and DTG 50mg film coated tablets for use among children who required dose adjustments in the P2019 parent study that cannot be achieved with the triple-agent fixed dose combination formulations. DTG 10mg and 25mg tablets will not be provided and must be supplied locally. Single entity ABC and 3TC are not considered IP, will not be provided by the study, and must be supplied locally. Deviations from this dosing table are allowed only if alternative dosing was approved and implemented within the P2019 parent study.

4.2.3. Weight based dose adjustments for all subjects

Weight for all subjects will be measured and recorded at each visit to verify the subject is receiving the appropriate dose based on the current dosing tables (Appendix 2). If a subject's weight change requires a dose adjustment, the dose adjustment should be made. The local PPD medical monitor must be notified, although approval for a weight-based dose adjustment is not required. Dose adjustments for weight decreases will only be made if the weight decrease persists for 2 consecutive study visits.

4.3. Type and Number of Subjects

All subjects from the P1093 and P2019 studies who meet the screening eligibility criteria and are unable to access age appropriate formulations of IP locally, will be allowed to enroll in this study and will be considered evaluable. Based on the design of the parent studies, a maximum of 300 pediatric subjects with HIV could enroll in this study.

4.4. Design Justification

A rollover study is needed in order to provide access to DTG or ABC/DTG/3TC FDC, until age appropriate formulations are approved locally and are available commercially or other availability occurs from another source (e.g. government programs, aid programs, assistance programs, etc.).

4.5. Dose Justification

The doses for this study have been determined by the results of the parent studies. Current weight-based dosing tables can be found in Appendix 2.

If new dosing for DTG or ABC/DTG/3TC is licensed during the conduct of this study, subjects will be allowed to switch to these doses as allowed by local practice.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG in the treatment of HIV-infected Adult and Pediatric subjects can be found in the most current version of the DTG Investigator's Brochure (IB) [ViiV Healthcare Ltd and local DTG product labeling]. The following section outlines the risk assessment and mitigation strategy for DTG in this protocol.

4.6.1. Risk Assessment for DTG

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1, 2]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
Hypersensitivity (HSR) and rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase 2b/3 clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for HSR (Section 12.6.1.4) and rash (Section 12.6.1.5). 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. For Grade 3/4 rash, except where the aetiology is clear and not associated with study drug or where there is a definitive diagnosis clearly attributable to a concomitant medication (and not to study drug) or to a concomitant infection, subjects must permanently discontinue study drug and be withdrawn from the study.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries.	Subjects meeting the following criteria during the screening period are excluded from participating (Section 5.2). • Alanine aminotransferase ≥5 times ULN or ALT 3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) Investigators should consult current treatment guidelines when considering choice of nucleoside reverse transcriptase inhibitor (NRTIs) for subjects with chronic HBV infection. Additional treatment considerations should be guided by local treatment guidelines. Adequate HBV therapy must be administered to subjects with chronic HBV infection (Section 12.6.1.8). Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 12.6.1.2).
Theoretical serious drug interaction with dofetilide pilsicainide and fampridine	Co-administration of DTG may increase dofetilide/pilsicainide/fampridine plasma concentration via inhibition of organic cation transporter 2, resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide/pilsicainide/fampridine is prohibited in the study (Section 6.11.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1, 2]
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviors are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar or favorable compared with other ART. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared to efavirenz (EFV)/ tenofovir (TDF)/emtricitabine (FTC) in ING114467; however, this was not duplicated in any other Phase 2b/3 study conducted with DTG.	Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality should be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour, which should be reported using a specific electronic Case Report Form (eCRF) module (Section 7.6.5). In addition, the subject informed consent form includes information on this risk of depression and suicidal ideation and behaviors.
Neural tube defects	In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was reported with exposure to DTG compared to non-dolutegravir containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking DTG-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-DTG containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI-0.03-0.30). In the same study, no increased risk of neural tube defects was reported in women who started DTG during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started DTG during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-DTG containing regimens during pregnancy.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3, Section 12.3.1) from 30 days prior to the first dose of study medication and until the last dose of study medication and completion of the Follow-up visit. 2. Females who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Females who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. Pregnancy status is monitored at every study visit

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1, 2]
1. Careful monitoring of all SAEs and AEs leading to treatment discontinuation will be conducted using relevant event reports and will be managed appropriately including, but not limited to, withdrawal of IP, and will be followed to resolution as per standard Medical Monitoring practices (See Section 7.6.1.1). 2. SAEs, AEs leading to treatment discontinuation and pregnancies will be routinely reviewed by PPD and ViiV Healthcare/GSK. This will include in-stream review of data from this clinical trial on a routine basis.		

4.6.2. Risk Assessment for ABC/DTG/3TC

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information on ABC/DTG/3TC		
Hypersensitivity (including abacavir hypersensitivity reaction) and rash	A well characterized, idiosyncratic, drug-related hypersensitivity reaction is the most important risk associated with ABC. Although the diagnosis of ABC HSR is based on clinical symptoms, exclusion of individuals found to carry the human leucocyte antigen (HLA)-B*5701 allele from ABC therapy reduces the risk of hypersensitivity reactions. Rash, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported in patients taking ABC. Hypersensitivity reactions have been observed uncommonly with DTG. Rash, generally mild to moderate in intensity, was commonly reported in DTG Phase 2b/3 clinical trials. No episodes of severe rash, such as Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme were reported. Data on hypersensitivity reactions for DTG and DTG+ABC/3TC fixed dose combination suggest that there will not be additional risk from a hypersensitivity reaction in HLA-B*5701 negative subjects receiving the ABC/DTG/3TC fixed dose combination.	Screening for the carriage of HLA-B*5701 is recommend when such screening is considered SoC. Subjects positive for HLA-B*5701 are excluded from participating. Additionally, subjects with history or presence of allergy to any of the study drugs or their components are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for suspected hypersensitivity reactions with DTG or ABC, and skin reactions without systemic involvement (Section 12.6.1.9). The subject informed consent form includes information on this risk and the actions subjects should take in the event of a hypersensitivity reaction or associated signs and symptoms. Subjects are to be reminded to read the ABC hypersensitivity reaction Warning Card provided, and of the importance of keeping this card with them at all times. All subjects in the P2019 parent study will have been screened negative for HLA-B*5701 at entry into that study.
Drug induced liver injury and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus and/or hepatitis C virus co-infection, improvements in immunosuppression because of HIV virologic and immunologic responses to DTG-containing antiretroviral therapy, along with inadequate therapy for hepatitis B virus co-infected subjects, likely contributed to significant elevations in	Subjects meeting any of the following criteria during the screening period are excluded from participating (Section 5.2) • Alanine aminotransferase ≥5 times ULN or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) • Unstable liver disease, cirrhosis and/or known biliary abnormalities (except for hyperbilirubinemia or jaundice due to Gilbert's syndrome or asymptomatic gallstones) • Subjects positive for hepatitis B virus in the parent study (hepatitis B virus surface antigen positive)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	liver chemistries. Current treatment guidelines do not recommend mono-therapy with 3TC for patients with hepatitis B virus infection. Additionally, discontinuation of 3TC in hepatitis B virus infected subjects can result in severe exacerbations of hepatitis B virus. For subjects co-infected with hepatitis C virus and HIV, [some] treatment guidelines recommend that the hepatitis C virus infection is treated first before starting treatment for the HIV. Additionally, interferon and/or ribavirin toxicity maybe frequent and difficult to differentiate causality from investigational product	• Subjects with anticipated need for HCV therapy with interferon or any drugs that have potential for adverse drug:drug interactions with study treatment throughout the entire study period. Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected drug induced liver injury or other clinically significant liver chemistry elevations (Section 5.4.4 and Section 12.4).
Theoretical serious drug interaction with dofetilide, pilsicainide and fampridine	Co-administration of DTG may increase dofetilide, pilsicainide or fampridine plasma concentration via inhibition of organic cation transporter 2, resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide, pilsicainide or fampridine is prohibited in the study (Section 6.11.2).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar or favourable compared with other antiretroviral therapies. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared to efavirenz/tenofovir/emtricitabine in the SINGLE clinical study; however, this was not duplicated in any other VH Sponsored Phase 2b/3 study with DTG or ABC/DTG/3TC.	Due to the elevated risk in the HIV-infected population, and reports in patients treated with integrase inhibitors, including DTG, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (Section 7.6.5).
Renal function	Lamivudine is eliminated by renal excretion and exposure increases in patients with renal dysfunction. ABC/DTG/3TC FDC should not be used in participants with creatinine clearance of less than 30 mL/min because, whilst	Known ≥Grade 3 laboratory toxicities (e.g. neutrophil count, hemoglobin, platelets, aspartate aminotransferase (AST), ALT, lipase, serum creatinine, eGFR and total bilirubin) would be considered exclusionary if identified at or after the penultimate parent study visit, prior to enrolment in the

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	no dosage adjustment of DTG or ABC is necessary in patients with renal impairment, dose reduction is required for the 3TC component.	study. Repeat testing is allowed for eligibility determination.' Participants who develop confirmed Grade 4 creatinine clearance (<30 ml/min/1.73m^2) should permanently discontinue study drug. Detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 5.4.3).

4.6.3. Benefit Assessment

DTG as an oral tablet formulation has been approved for the treatment of HIV infection in most countries around the world and is recommended as a component of first line therapy in global treatment guidelines (DHHSa, 2019; EACS, 2018; WHO, 2018). In June 2020, the US FDA expanded the use of the already approved DTG 50 mg film-coated tablet to pediatric patients weighing at least 20 kg and approved the DTG dispersible tablet for oral suspension for children as young as four weeks of age and weighing at least 3 kg.

Data from the P1093 parent study are presented in the DTG IB. The safety, pharmacokinetics and effectiveness of Tivicay and Tivicay PD were evaluated in P1093, in 75 HIV-1 infected, treatment-naïve or treatment experienced, INSTI-naïve pediatric and adolescent subjects aged 4 to less than 18 years weighing at least 3 kg. Additional pharmacokinetics data were evaluated in 2 pharmacokinetic sub studies in ODYSSEY, an open-label randomized, non-inferiority trial to evaluate the safety, efficacy and, pharmacokinetic parameters of DTG plus 2 NRTIs compared with SoC in HIV-1 infected pediatric subjects younger than 18 years.

Overall, the safety data in pediatric subjects from P1093 were comparable to those observed in adults. The pharmacokinetic parameters of Tivicay or Tivicay PD in pediatric subjects from P1093 and ODYSSEY were comparable to those of adults receiving 50 mg once daily or twice daily. The effectiveness observed in P1093 is comparable to that of treatment experienced adult subjects.

Safety and effectiveness of Tivicay or Tivicay PD have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 kg or in any pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir). The ABC/DTG/3TC FDC, approved in multiple countries worldwide for the treatment of HIV-1 infection, provides a convenient once-daily single tablet regimen, without need for a PK booster or food/fluid restrictions, and with limited safety implications resulting from theoretical or actual drug: drug interactions compared with other antiretroviral agents (including EFV and those requiring a PK booster).

4.6.4. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risks to subjects participating in this study, the potential risks identified in association with long-term use of DTG based combination ART are justified by the anticipated benefits that may be afforded to HIV-1 infected pediatric subjects continuing DTG-containing regimens as part of this study.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on DTG that may impact subject eligibility is provided in the current DTG IB.

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

5.1. Inclusion Criteria

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. Subjects must have completed participation in one of the following parent studies, for the duration noted: • P1093 parent study through at least Week 180 • P2019 parent study through at least Week 48. 2. Virological control at screening: a) Subjects in parent study P1093 must have virological control defined as HIV-1 RNA <400 c/mL at their penultimate visit (on or after the Week 180 visit). b) Subjects in parent study P2019 must have virological control defined as HIV-1 RNA <200 c/mL at their penultimate visit (on or after Week 36). **Note:** ▪ If the penultimate P1093; P2019 visit (on or after Week 180 for P1093; on or after Week 36 for P2019) indicates the possibility of virologic failure, a single retest can be completed in the parent study. – Results of the retest must be obtained and confirmed prior to the Day 1 visit (the Day 1 visit overlaps with the final visit in each parent study). – If the retest indicates virologic control is present as noted above, eligibility is confirmed as long as the participant meets all other entry criteria. – Adherence issues should be addressed, and viral suppression must be confirmed prior to Day 1. 3. Evidence of continued benefit from IP during the subject's participation in the parent study (P1093 or P2019). – At screening, Investigators will submit a clinical summary verifying evidence of continued benefit from IP during the subject's participation in the parent study (P1093 or P2019). – The summary will be submitted via the PPD ePIP system to the Study Medical Monitor who will review and confirm if the inclusion criterion has been met. – Confirmation from the Study Medical Monitor is required to meet this eligibility criterion
SEX
4. Males and Females All subjects who are engaging in sexual activity should be counselled on safer sexual

practices including the use and benefit/risk of effective barrier methods (e.g. male condom) and on the risk of HIV transmission to an uninfected partner.

Females:

Female subjects who are of childbearing potential and who are engaging in sexual activity that could lead to pregnancy, must agree to use one of the acceptable birth control methods listed in Appendix 3 (Section 12.3) until the last dose of study medication and completion of the Follow-up visit (4 weeks after the last dose). Condoms are recommended in addition, because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

INFORMED CONSENT
5. Parent or legal guardian or subject ≥18 years of age is able and willing to provide signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Where applicable, subjects must provide written assent.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Confirmed virologic failure with evidence of resistance to: a) DTG in the P1093 parent study, or b) ABC, DTG or 3TC (with the exception of M184V) in the P2019 parent study
2. Presence of any active Acquired Immunodeficiency Syndrome (AIDS) defining opportunistic infection.
3. Known ≥Grade 3 laboratory toxicities (e.g. neutrophil count, hemoglobin, platelets, aspartate aminotransferase (AST), ALT, lipase, serum creatinine, eGFR and total bilirubin) would be considered exclusionary if identified at or after the penultimate parent study visit, prior to enrollment in the study. Repeat testing is allowed for eligibility determination. NOTE: ≥Grade 3 total bilirubin is allowable, if the subject is on ATV. NOTE: Subjects with laboratory abnormalities considered unrelated to IP may be allowed to enter the study. Thus, if the laboratory abnormality persists upon repeat testing, the subject may be considered for study entry after consultation and approval of the study team. An exception to this note is for participants with confirmed creatinine clearance of less than 30 mL/min in which DTG/ABC/3TC FDC should

not be used.

4. Previous permanent discontinuation from IP in the parent study due to toxicity, intolerance, or pregnancy.
5. Known ALT ≥5xULN, OR ALT ≥3xULN AND bilirubin ≥1.5xULN (with >35% direct bilirubin) would be considered exclusionary if identified at or after the penultimate parent study visit, prior to enrolment in the study. Subjects with moderate to severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification should be excluded.
6. Subjects positive for hepatitis B virus at any time prior to entry (hepatitis B virus surface antigen positive).
7. Females who are pregnant or plan to become pregnant or breastfeed during the study.
8. Subject is currently participating in or has participated in a study with a compound or device that is not commercially available within 30 days of signing informed consent, unless permission from the PPD Medical Monitor is granted.
9. Presence of any history of allergy/sensitivity to any of the study drugs.
10. Subjects transitioning from the P2019 study (taking ABC/DTG/3TC) who are HLA-B*5701 positive based on documented testing at any time prior to entry.

CONCOMITANT MEDICATIONS
11. Use of any disallowed medications at time of screening (see Section 6.11.3 for a complete list of disallowed medications). 12. Anticipated need for HCV therapy with interferon or any drugs that have potential for adverse drug:drug interactions with study treatment throughout the entire study period.

RELEVANT HABITS
13. Subject is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

CONTRAINDICATIONS
14. Clinical or symptomatic evidence of pancreatitis, as determined by the clinician

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
15. Any condition (including but not limited to alcohol and drug use) that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

When there is a country specific label with an approved pediatric indication(s), please refer to the Local Product Information for Tivicay (DTG) or Triumeq

(ABC/DTG/3TC) for information on contraindications and drug interactions when making decisions about patient eligibility.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the study but do not meet inclusion/exclusion criteria.

5.4. Withdrawal/Stopping Criteria

5.4.1. Criteria for Study Discontinuation

- The subject or legal guardian refuses further treatment and/or follow-up evaluations.
- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The subject requires treatment with medications that are disallowed while on this study.
- Non-adherence of medications including IP and/or background therapy as determined by Investigator.
- The investigator or study medical monitor in consultation with the PPD Medical Monitor has determined that there would be no benefit to continue on-study and receive IP.

Note: The Sponsor (ViiV Healthcare) advises against continuation of IP after confirmed VF due to the risk of INSTI resistance development.

5.4.2. Criteria for IP Discontinuation

- Pregnancy (intrauterine), regardless of termination status of pregnancy (see Section 7.6.2). As a reminder, females of reproductive potential who change their minds and desire to be pregnant should also be withdrawn from the study.
- New data become available that indicate IP should be discontinued.
- Drug toxicity that requires permanent IP discontinuation.
- Liver toxicity where stopping criteria specified in Section 5.4.4 are met and no compelling alternate cause is identified.
- Allergic reaction or rash criteria as specified in Section 12.6.1.4 and Section 12.6.1.5, respectively, are met and no compelling alternate cause is identified.
- The investigator determines that further participation would be detrimental to the subject's health or well-being.

NOTE: In the event of treatment discontinuation, subjects will be asked to continue on study for 4 weeks after they discontinue IP and complete the Follow-up Visit. If an AE remains unresolved at the Follow-up Visit, the subject will continue to be followed until the AE resolves.

A subject may withdraw from IP at any time upon the request of the parent(s)/guardian(s) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. In addition, investigators should attempt to record the reason for withdrawal in the patient records. A Study Discontinuation eCRF must be completed.

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

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

5.4.3. Management of Renal Toxicity

DTG can inhibit the tubular secretion of creatinine and can therefore be associated with a slight increase in serum creatinine and apparent decrease in the estimated glomerular filtration rate (generally by 10% or less). This typically occurs within the first four weeks of treatment with DTG and remains stable thereafter and is not associated with renal damage or true decline in renal function. See below for advice on management of renal toxicity by DAIDS grading.

Note: Utilize absolute creatinine or creatinine clearance value when determining the respective DAIDS severity bands.

When serum creatinine testing is performed, it is recommended that the eGFR rate should be calculated using the bedside Schwartz formula:

eGFR (mL/min/1.73 m^2) = 0.413 * height (in cm) ÷ serum creatinine (in mg/dL)

Both the serum creatinine level and the eGFR rate should be graded for severity and assessed for change from baseline and clinical significance. When abnormal results are obtained, confounding factors and other non-study drug explanations (e.g., concomitant medications, concomitant illness, dehydration etc.) should be considered and a nephrology consult may be obtained.

5.4.3.1. Creatinine

It is recommended that subjects who experience an increase to Grade 2 from a normal or Grade 1 serum creatinine level at baseline, or an increase to Grade 3 from a normal,

Grade 1 or Grade 2 creatinine level at baseline may continue study treatment but should undergo confirmatory testing within 2-4 weeks. Participants who develop a Grade 4 creatinine level should have study treatment temporarily held and have confirmatory testing within 2 weeks. Serum creatinine testing should be repeated, and consideration should also be given to performing a urinalysis assessing urine albumin:creatinine and urine protein:creatinine ratios and if the elevation is confirmed, the Study Medical Monitor should be consulted regarding further follow-up and management.

If the increase to Grade 3 creatinine is confirmed, study drug should be temporarily held and the Study Medical Monitor should be consulted regarding further follow-up and management.

Consideration should be given to a nephrology consultation, and the case discussed with the Study Medical Monitor to determine benefit risk of continuing with study drug.

For a confirmed Grade 4 creatinine, study drug should be permanently discontinued

Participants requiring permanent discontinuation of study drug should be followed weekly until resolution and have withdrawal study evaluations completed. A follow up visit should be performed 4 weeks after the last dose of study drugs.

5.4.3.2. eGFR

It is recommended that subjects who experience an increase from a normal, Grade 1, or Grade 2 eGFR at baseline to Grade 3 eGFR rate may continue study treatment but should undergo confirmatory testing within 2-4 weeks. Participants who develop a Grade 4 eGFR should have study treatment temporarily held and have confirmatory testing within 2 weeks. Other signs of renal toxicity should be sought and any alternative cause of renal impairment should be explored and treated appropriately. Consideration should also be given to assessing cystatin C and performing a urinalysis assessing urine albumin:creatinine and urine protein:creatinine ratios.

If the increase to Grade 3 eGFR is confirmed, study drug should be temporarily held and the Study Medical Monitor should be consulted regarding further follow-up and management.

Consideration should be given to a nephrology consultation, and the case discussed by the study team to determine benefit risk of continuing with study drug.

For a confirmed Grade 4 eGFR study drug should be permanently discontinued.

Participants requiring permanent discontinuation of study drug should be followed weekly until resolution and have withdrawal study evaluations completed. A follow up visit should be performed 4 weeks after the last dose of study drugs.

5.4.4. Liver Chemistry Stopping Criteria

When there is a country specific label with an approved pediatric indication(s), please refer to the Local Product Information for Tivicay or Tivicay PD (DTG) or Triumeq (ABC/DTG/3TC) for information on the monitoring of liver function. In

other cases, recommendations for drug discontinuation during treatment are given below.

In the event of a clinical picture suggestive of potential liver injury in a patient taking IP, patients must be investigated as clinically indicated. Failure by an investigator to monitor liver safety could impact on the continuation of the patient in this study.

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and proper evaluation of liver event etiology during administration of IP and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance).

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

For any subject meeting one of the criteria outlined in Table 1 or Table 2, or if the Investigator believes that it is in the best interest of patients, the Investigator must follow the actions noted below Recommended follow up assessments are also outlined in Table 1.

Table 1 Liver Chemistry Stopping Criteria- Liver Stopping Event

ALT absolute	*ALT ≥ 8xULN*
ALT increase	*ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)*
Bilirubin[1, 2]	*ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)*
INR[2]	*ALT ≥ 3xULN **and** International normalised ratio (INR)>1.5, if INR measured*
Cannot Monitor	*ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks* *(See Table 2 for actions where subjects CAN be monitored weekly for >2 weeks)*
Symptomatic[3]	*ALT ≥ 3xULN (if baseline ALT is ≤ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity* *ALT ≥ 3x baseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity*

Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	***Recommended Follow Up Assessments***
• **Immediately hold IP.** • **If a causal relationship between the liver event and IP cannot be ruled out, then IP must be permanently discontinued and the Subject not rechallenged due to the risk of a recurrent reaction**. • Report the event to the PPD by telephone within **24 hours**. • Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to PPD as serious adverse events using the serious adverse event case report form. • Complete the liver event case report form for all events meeting liver stopping criteria, and submit to PPD within one week of first becoming aware of the event • Liver event follow up assessments are recommended. • Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline	• Viral hepatitis serology, including: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and hepatitis B core antibody; Hepatitis C RNA; Hepatitis E IgM antibody. • Cytomegalovirus IgM antibody. • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing). • Syphilis screening. • Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form Serum acetaminophen adduct High Performance Liquid Chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must

(see **MONITORING** below). • **If the liver event has a clear underlying alternative cause, other than drug-induced liver injury, then Drug Restart may be considered by ViiV (for exception see** Section 12.5**).** • If restart is **not allowed or not granted**, permanently discontinue IP and may continue subject in the study for any protocol specified follow up assessments. **MONITORING:** • It is recommended that the site make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments described to the right. • A specialist or hepatology consultation is recommended. • It is recommended that the site monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline.	contact the medical monitor when this test is required. **NOTE: not required in China** • Serum creatinine kinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin ≥1.5xULN. • Complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Liver Imaging and/or Liver Biopsy data will be collected in the case report form. • Record use of concomitant medications within the site source documentation, including acetaminophen, herbal remedies, other over the counter medications.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue IP for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia). Record the appearance or worsening of any such clinical symptoms on the adverse event report form if the adverse event has led to discontinuation of treatment.

Table 2 Liver Chemistry Increased Monitoring Criteria

Criteria	Actions
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for >2 weeks.	• Notify the PPD medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue IP • It is recommended that the subject return weekly for repeat liver chemistries (ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) until resolution, stabilisation (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above

5.4.5. Study Treatment Restart and Rechallenge

'**Rechallenge**' refers to resuming study treatment following drug induced liver injury (DILI). Following DILI, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

In the event of a discontinuation of IP for a Liver Stopping Event, subjects **should not be rechallenged** with IP due to the risks associated with rechallenge.

'Drug restart' refers to resuming study treatment following a Liver Stopping Event in which there is a clear underlying cause (other than drug induced liver injury) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis).

If subject meets liver chemistry stopping criteria, do not restart subject with IP unless:

- ViiV Healthcare Safety and Labeling Committee (VSLC) approval **is granted**
- Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart is signed by the subject

If VSLC approval to restart subject with study treatment **is not granted**, then subject must permanently discontinue IP and may continue in the study for protocol-specified follow up assessments.

For detailed guidance, refer to:

- Section 12.4 (Appendix 4) Liver Safety Treatment Restart Guidelines
- Section 12.5 (Appendix 5) "Checklist for Drug Restart Approval or Refusal".

5.5. Subject and Study Completion

A completed subject is one who has attended all study visits and has either transitioned to an available age appropriate formulation of DTG or ABC/DTG/3TC or has otherwise withdrawn from the study (See Section 5.4 for complete details on study withdrawal).

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

Investigational Product (IP) is defined as DTG film coated tablets, DTG DT, ABC/DTG/3TC immediate release tablets or ABC/DTG/3TC DT. IP for subjects transitioning from parent studies P1093 and P2019 will be provided through the study as per DTG and ABC/DTG/3TC dosing tables (Appendix 2). Other ARVs will not be provided by the study and are not considered part of the study. These other ARVs must be supplied locally.

Single entity DTG, in age appropriate formulations, will be provided to eligible subjects transitioning from parent study P1093. Sites participating in P1093 and this rollover study are in the following countries: Botswana, Brazil, Kenya, South Africa, Tanzania, Thailand, Uganda, United States and Zimbabwe.

ABC/DTG/3TC, in age appropriate formulations, will be provided to eligible subjects transitioning from parent study P2019. Sites participating in P2019 and this rollover study are in the following countries: Botswana, South Africa, Thailand and the United States.

6.1.1. Medical Devices

- Medical devices are not supplied or manufactured by GSK/ViiV for use in this study. The devices described below were supplied by ViiV/GSK for DAIDS sponsored P1093, and P2019 parent studies. Equivalent medical devices (size and material of construction) will be sourced locally by each site for use in this 205858 study:

  For subjects transitioning from the P1093 parent study:
  - Polypropylene dosing cup with graduation marks at 5 mL and 10 mL
  - Polypropylene oral Dosing Syringe 5 mL or 10 mL

  For subjects transitioning from the P2019 parent study:
  - Polypropylene Dosing cup with graduation marks at 15 mL, 20 mL, 25 mL, 30 mL
  - Polypropylene Oral Dosing Syringe 25 mL

- Instructions for medical device use are provided within the Study Pharmacy Manual.

6.2. Treatment Assignment

The IP will be administered in an open-label fashion in this study. Informed consent must be obtained prior to any study procedures.

6.3. Planned Dose Adjustments

Weight in kilograms (Kg) will be measured and recorded at each visit to verify whether the subject is receiving the appropriate formulation and dose based on the current dosing tables; see Appendix 2. If a subject's weight change requires a dose adjustment, the dose adjustment should be made and the local PPD medical monitor must be notified, although team approval for a weight-based dose adjustment is not required. Dose adjustments for weight decreases will only be made if the weight decrease persists for 2 consecutive study visits.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage

- Under normal conditions of handling and administration, none of the study IP formulations are expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK (on behalf of ViiV Healthcare) upon request.
- All formulations must be stored in a secure area under the appropriate physical conditions described below. Access to and administration of the IP will be limited to the investigator and authorized site staff.
- The investigator or designee should confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported to PPD and resolved before use of the IP.

6.5.1. DTG Film-Coated Tablets

DTG **film coated tablets** are available as 50 mg tablets. Store at 15ºC to 30ºC (59ºF to 86ºF). Dispense and store only in the original manufacturer's container. If provided, the desiccant should remain in the bottle.

No special preparation of study treatment is required.

6.5.2. DTG Dispersible Tablets

Dolutegravir **5 mg pediatric DTs** are white, round, film-coated tablets for oral administration. The tablets are debossed with 'SV H7S' on one side and '5' on the opposite side. The tablets contain 5.26 mg of dolutegravir sodium which is equivalent to 5 mg dolutegravir free acid. The tablets are packed into high density polyethylene (HDPE) bottles with child resistant closures that include an induction seal. The bottles contain a desiccant. Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant. In the study site pharmacy, store up to 30°C (86°F).

Dolutegravir DTs will be dispersed in drinking water for oral administration. Caregivers will be instructed to disperse the appropriate number of dispersible tablets in the volume of water shown in Table 3. Once dispersed, the medication should be consumed, as soon as possible, but no longer than 30 minutes after reconstitution. After the medication is consumed, another 5 mL of water should be added to the cup, swirled and provided to the subject. If any medicine remains, repeat the instructions above to ensure the subject receives the full dose.

Table 3 Dispersion Volumes for DTG Dispersible Tablets

Number of Tablets per Dose	Dispersion Volume
1	5 mL
2	
3	
4	10 mL
5	
6	

6.5.3. ABC/DTG/3TC Dispersible Tablets

ABC 60 mg/DTG 5 mg/3TC 30 mg pediatric dispersible tablets are pale yellow, biconvex, oval, film-coated, debossed with 'SV WTU' on one side and plain on the opposite side. Each tablet contains 70.2 mg abacavir sulfate, which is equivalent to 60 mg of abacavir free base; 5.26 mg dolutegravir sodium, which is equivalent to 5 mg of dolutegravir free acid; and 30 mg of lamivudine. The tablets are packaged in HDPE bottles with child-resistant closures that include an induction seal and a desiccant. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. In the study site pharmacy, store up to 30°C (86°F).

ABC/DTG/3TC dispersible tablets will be dispersed in water for oral administration. Caregivers will be instructed to disperse the appropriate number of dispersible tablets in the volume of water shown in Table 4. For children in weight band #3 (14 to less than 20 kg) or #4 (20 to less than 25 kg) who report poor palatability and/or acceptability, caregivers will be provided the option of dispersing the appropriate number of dispersible tablets in the volume of water shown in Table 5. Once dispersed, the medication should

be consumed, as soon as possible, but no longer than 30 minutes after reconstitution. After the medication is consumed, another 15 mL of water should be added to the cup, swirled and provided to the subject. If any medicine remains, repeat the instructions above to ensure the subject receives the full dose.

Table 4 Dispersion Volumes for ABC/DTG/3TC Dispersible Tablets

Weight Band		Number of Dispersible Tablets per Dose	Dispersion Volume
#1	6 to less than 10 kg	3	15 mL
#2	10 to less than 14 kg	4	20 mL
#3	14 to less than 20 kg	5	20 mL
#4	20 to less than 25 kg	6	20 mL

Table 5 Alternate Dispersion Volumes for ABC/DTG/3TC Dispersible Tablets

Weight Band		Number of Dispersible Tablets per Dose	Dispersion Volume
#1	6 to less than 10 kg	3	15 mL
#2	10 to less than 14 kg	4	20 mL
#3	14 to less than 20 kg	5	25 mL
#4	20 to less than 25 kg	6	30 mL

6.5.4. ABC/DTG/3TC Immediate Release (Triumeq) Tablets

ABC/DTG/3TC immediate release (Triumeq) tablets are purple, biconvex, oval, film-coated, debossed with “572 Tri” on one side, and plain on the opposite side. Each tablet contains 702 mg abacavir sulfate, which is equivalent to 600 mg of abacavir free base; 52.62 mg dolutegravir sodium, which is equivalent to 50 mg of dolutegravir free acid; and 300 mg of lamivudine. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. In the study site pharmacy, store at 25°C (77°F) with excursions between 15° and 30°C (59° to 86°F) permitted (See USP Controlled Room Temperature). For any child who is not able to swallow whole immediate release tablets, the tablets can be crushed and mixed with a liquid or semi-solid food such as applesauce or mashed banana.

6.6. Product Accountability and Disposal

The site investigator is responsible for ensuring that all accounting of IP supplies occurs in accordance with all local regulatory requirements. This includes accounting for IP supplies received, dispensed, and destroyed as necessary. All unused supplies should be destroyed by the investigator or designee (e.g., site pharmacist) in accordance with national and/or local regulations, with the exception of investigators located in the US (See Section 6.6.1).

NOTE: It is important that IP is dispensed to the subject for whom the supplies were requested and approved, and to no other patient; this is required in order to ensure compliance with the regulatory requirements.

6.6.1. Special Precautions in the US for Disposal

Any unused IP should be disposed of in accordance with local requirements; however, investigators in the US must return any unused IP according to the Pharmacy Manual.

6.7. Compliance with Study Treatment Administration

A record of the number of IP tablets dispensed to, and taken by, each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will be recorded in the eCRF.

6.8. Management of Study Treatment Overdose

Any tablet intake exceeding the daily number of IP tablets will be considered an overdose. For the purposes of this study, an overdose is not an AE unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is an SAE (See Section 12.7.2) and must be reported. The investigator should use clinical judgment in treating overdose, as PPD or ViiV Healthcare/GSK are unable to recommend specific treatment.

6.9. Treatment after the End of the Study

Study drug will be provided until age-appropriate formulations receive local regulatory approval and are commercially available, or are available from some other source (e.g. government programs, aid programs etc.), or until subjects no longer derive benefit from treatment, or until a subject meets a protocol defined criteria for discontinuation, or until development of DTG, or ABC/DTG/3TC is terminated.

Subjects will not receive any additional treatment from ViiV Healthcare after completion of the study because all subjects will transition from the study to age appropriate available and approved sources of the IP.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not ViiV Healthcare/GSK is providing specific post-study treatment.

6.10. Meals and Dietary Restrictions

IP can be administered with or without food.

6.11. Concomitant Medications and Non-Drug Therapies

Patients should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and IP.

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject and their physician.

If HIV-1 RNA levels are being followed per the local SOC, it is highly recommended that any vaccine, if necessary, be given during or immediately after a scheduled visit after any laboratory tests have been drawn. This is because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA.

6.11.1. Permitted Medications

Concomitant medications (prescription and non-prescription) will be permitted during the course of the program at the investigator's discretion (except for prohibited medications described in Section 6.11.3) and should be administered only as medically necessary.

Approved hormonal contraception may be administered with IP. However, the investigator should consult local prescribing information for guidance on the use of hormonal contraceptives with background ART as some ARVs have clinically significant drug interactions with these products.

IP should be administered 2 hours before or 6 hours after taking antacid or laxative products or sucralfate containing polyvalent cations (e.g. aluminium and magnesium) or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Iron supplements can be taken with IP provided that all are taken together with a meal. Under fasted conditions, IP should be given 2 hours prior to OR 6 hours after iron supplements.

Metformin concentrations may be increased by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG with metformin, to maintain glycemic control.

Clinical monitoring is recommended for subjects taking methadone, as methadone maintenance therapy may need to be adjusted in some subjects.

If any treatments for Coronavirus Disease – 2019 (COVID-19) are planned for a study subject, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains

appropriate. Refer to Section 12.8 (Appendix 9 COVID-19 Pandemic and Study Guidance) for safety reporting requirements and instruction for data capture.

It is the responsibility of the investigator to check on potential drug-drug interactions between background ART and other concomitant therapies, before placing a subject on a specific medication.

6.11.2. Concomitant Medications Necessitating DTG Dose Adjustment

Antiviral Agents

When constructing a subject's background ART regimen, other integrase inhibitors (i.e. RAL, elvitegravir [EVG]) are prohibited because no PK, safety or efficacy data about co-administration are available.

Additionally, the pediatric weight-based once daily dose of DTG **must be administered twice daily with the following antiviral agents** because they have been shown or have the potential to decrease plasma DTG concentrations;

- efavirenz (EFV),
- nevirapine (NVP),
- tipranavir/ritonavir (TPV/RTV),
- and etravirine (ETR) – without boosted protease inhibitors.

Note: ETR can be dosed at the once daily pediatric dose when co-administered with lopinavir/RTV, DRV/RTV or ATV/RTV (these boosted protease inhibitors have been shown to counteract ETR enzyme induction).

Other Agents

Additionally, the pediatric weight-based once daily dose of DTG **must be administered twice daily with the following other agents** because they have known for potential enzyme induction activity;

- rifampicin –(See Appendix 6, Section 12.6.1.7)
- carbamazepine
- phenytoin
- phenobarbital (barbiturates)
- St. John's wort

6.11.3. Prohibited Medications

When constructing a subject's background ART regimen, other integrase inhibitors (i.e. RAL, elvitegravir [EVG]) are prohibited because no PK, safety or efficacy data about co-administration are available.

Dofetilide, pilsicainide or fampridine must NOT be administered concurrently with DTG because DTG may inhibit the renal tubular secretion of dofetilide/pilsicainide/fampridine resulting in increased dofetilide/pilsicainide/fampridine concentrations and the potential for toxicity.

6.11.4. Additional considerations for ABC/DTG/3TC

Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving ABC/DTG/3TC FDC led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy participants. Riociguat dose may need to be reduced, consult the riociguat product labelling for dosing recommendations.

The pediatric weight based once daily dose of the single entity DTG (based on weight band dosing of ABC/DTG/3TC as noted in Section 12.2.3 Dosing Table) should be administered twice daily when ABC/DTG/3TC is co-administered with certain enzyme inducing drugs.

- Liquid medications containing sorbitol or other sugar alcohols (e.g., mannitol, xylitol, maltitol, isomalt) should be avoided as these excipients, which are used to sweeten pediatric liquid formulations, have been shown to reduce 3TC concentrations [Adkinson, 2018]. Site investigators should carefully review all liquid concomitant medications received by enrolled subjects. If any such medications are not clinically indicated, they should be discontinued. Otherwise, they should be switched to a solid dosage form when possible or to a liquid formulation that does not contain sorbitol or other sugar alcohols. Site investigators should be particularly cognizant of liquid cotrimoxazole formulations, which tend to contain high concentrations of sorbitol and are commonly used in HIV-infected children.

When there is a country specific label with an approved pediatric indication(s), please refer to the Local Product Information for Tivicay (DTG) or Triumeq (ABC/DTG/3TC) for information on drug:drug interactions.

7. STUDY ASSESSMENTS AND PROCEDURES

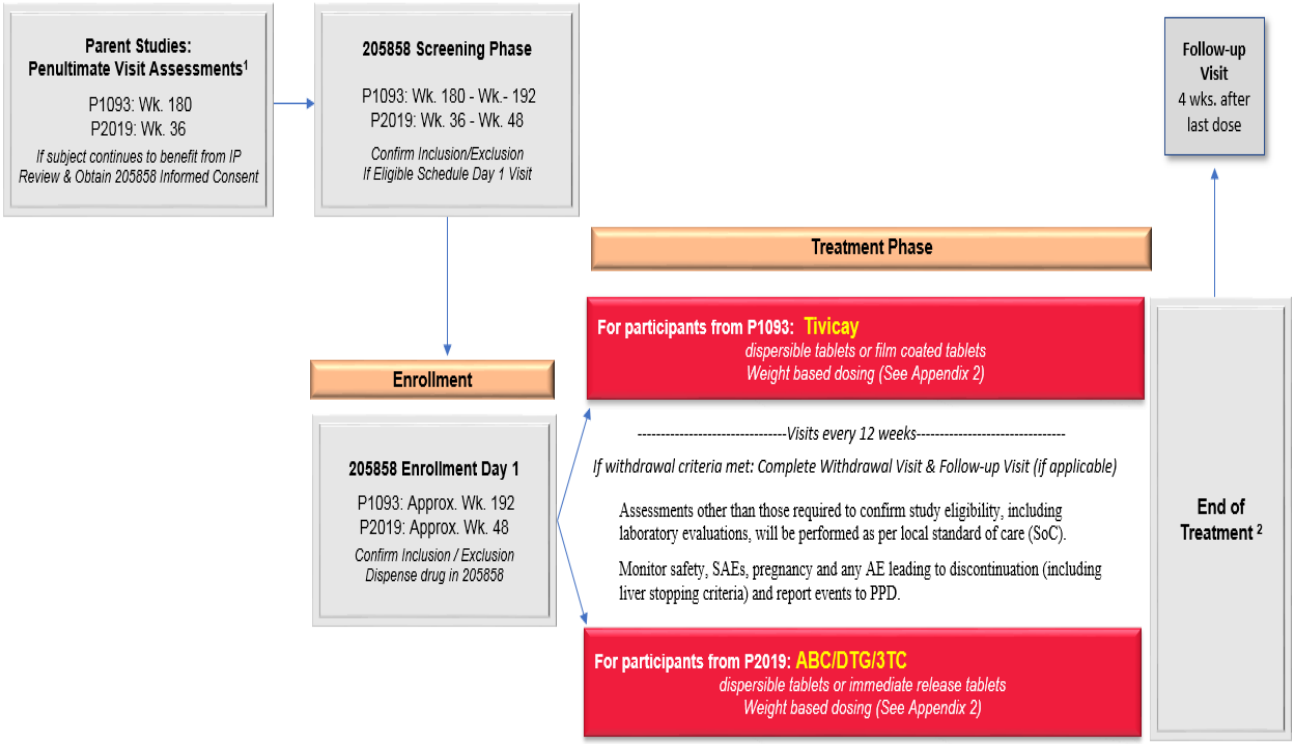
Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.2.

The following points must be noted:

- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the local PPD medical monitor and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

7.1. Study Schematic



1. See Penultimate Visit Assessments in Section 7.1.1

2. Study drug will be provided until age-appropriate formulations receive local regulatory approval and are commercially available or are available from some other source (e.g. government programs, aid programs etc) or until the subject no longer derives benefit from treatment or until a subject meets a protocol defined reason for discontinuation or until development of DTG or ABC/DTG/3TC is terminated.

7.1.1. Parent Studies: Penultimate Visit Assessments

Parent Studies: Penultimate Study Visit Assessments (refer to parent protocols for details)	**P1093**	**P2019**
Penultimate Visit	Week 180	Week 36
Screening Period (approximate)	Week 180-Week 192	Week 36-Week 48
Clinical Evaluations		
Medical History (review of existing and new conditions)	X	X
Review/update Adverse Events	X	X
Medication History (review of ongoing and new concomitant medications)	X	X
Physical Exam	X	X
Laboratory Evaluations		
HIV-1 RNA PCR	X	X
Pregnancy Test (blood or urine as per local SoC)	X	X
CBC with differential and platelets	N/A	X
ALT, AST, total bilirubin, direct bilirubin, creatinine, eGFR (bedside Schwartz)	N/A	X
Additional evaluations if clinically indicated	X	X
Dispense IP within Parent Study		
Penultimate Visit: Dispense Parent Study IP	X	X
Informed Consent for 205858		
If subject is benefiting from IP, obtain informed consent for 205858	X	X
If 205858 informed consent provided: Begin Screening phase: Confirm eligibility criteria for 205858 have been met	X	X

7.2. Time and Events Table

Table 6 Time and Events Table

Event	Screening Visit[1]	Day 1 Visit[2]	Every 12 Weeks	Withdrawal Visit	Follow-Up (post-SAE)
Visit windows			±4 Weeks	±4 Weeks	±4 Weeks
Informed consent	X				
Demographics		X			
Pregnancy test[3]	X	X		X	
Adverse events[4]		X	X	X	X
Serious adverse events[5]	X	X	X	X	X
Dispense DTG or ABC/DTG/3TC[6]		X	X		
Weight	X	X	X	X	
Inclusion/exclusion criteria	X	X			

1. The Screening visit corresponds to the penultimate visit of the parent studies. In most cases, this will correspond with the Week 180 visit of the P1093 study or the Week 36 visit of the P2019 study.
2. In most cases, the Day 1 visit will be the same as the final visit for the parent study (i.e. at or beyond Week 192 of the P1093 study or at or beyond Week 48 of the P2019 study).
3. Pregnancy test for females of childbearing potential only. Urine pregnancy test must be used at Day 1 and final/withdrawal visit. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
   At every visit (or some other more frequent interval), pregnancy prevention will be discussed with the subjects, including specific counselling, provision of information and advice as needed. Verbal confirmation of the use of an acceptable birth control option listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Appendix 3 Section 12.3.1 should be obtained. This discussion should be documented in the subject's study record.
   A pregnancy test should also be performed prior to IP re-administration, when dosing is disrupted for more than 7 days.
4. Only AEs leading to treatment discontinuation will be collected.
5. Only SAEs related to study participation will be collected from the time of informed consent signature and administration of study drug at Day 1. Other SAEs occurring between the time of informed consent signature and administration of study drug at Day 1 will be captured in the DAIDS sponsored parent studies.
6. Subjects transitioning from P1093 parent study will receive age appropriate formulations of DTG; Subjects transitioning from P2019 parent study will receive age appropriate formulations of FDC ABC/DTG/3TC.

7.3. Screening Visit

Subjects will sign a new consent specific to this rollover protocol at the Screening visit which corresponds to the penultimate visit of the parent studies (approximately Week 180 for most subjects transitioning from P1093 and Week 36 for most subjects transitioning from P2019).

During the Screening visit, the following are captured in the database (PPD eCRF):

- Informed Consent.
- Verification that the subject meets the inclusion/exclusion criteria.
- The subject's weight
- Confirmation of virologic suppression (HIV-1 RNA) (Section 5.1).

- A negative pregnancy test result for females of childbearing potential.
- Any SAE
- Study treatment, dose and formulation taken by subject.

Note: On the day of the Screening visit, HIV-1 RNA viral load and pregnancy testing will be performed as part of the parent studies. HIV-1 RNA results will be recorded in the eCRF and pregnancy test results will be documented in the source notes.

After eligibility has been verified, the investigator can request a 3-month supply of IP from PPD.

7.4. Day 1 Visit

The following will be obtained at the Day 1 visit and entered into the database (PPD eCRF):

- Any modification to DTG or ABC/DTG/3TC dose or formulation at this visit or since the last visit.
- Demographic parameters: year of birth, sex, race and ethnicity
- Confirmation that the subject continues to meet inclusion and no exclusion criteria.
- Weight
- Pregnancy test results for females of childbearing potential
- Plasma HIV-1 RNA viral load (as collected per local SOC)
- All SAEs
- All AEs leading to treatment discontinuation
- Confirmation that the subject is expected to return for the next quarterly visit.

The following will be obtained at the Day 1 visit per the local SOC, either directly or from the patient's medical records and **retained in the patient's medical records but will not be entered into the database (PPD eCRF)**: Medical history and physical exam (medical/medication/family history will be assessed as related to inclusion criteria listed in Section 5); review of changes in concomitant medications and background ART; assessment of any adverse events since last parent study visit (all SAEs and all AEs that lead to the discontinuation of IP will be captured in the database); lymphocyte subsets; lipid profiles and liver chemistry test results.

7.5. Patient Monitoring

7.5.1. Regular Visits (Every 12 Weeks)

The following will be obtained **every 12 weeks** and entered into the database (PPD eCRF):

- Any modification to DTG or ABC/DTG/3TC dose or formulation at the current visit or since the last visit.

- Weight
- Plasma HIV-1 RNA viral load (as collected per local SOC)
- Any SAE
- Any AE leading to treatment discontinuation
- Confirmation that the subject is expected to return for the next quarterly visit.

The following assessments are suggested to be performed per local SOC and if performed, **should be recorded in the investigator's patient records; these results if collected will not be entered into the database (PPD eCRF)**: Results of any laboratory chemistry/hematology, lipid profiles and CD4+ counts per local practice; history and physical exam; changes in concomitant medications and background ART; and confirmation of effective contraception in females of childbearing potential.

7.5.2. Study Withdrawal/Discontinuation

Subjects may be withdrawn from the study for any of the reasons outlined in Section 5.4.

The following assessments are to be performed per local SOC at the withdrawal visit (if different from a regular scheduled visit) and will be reported and entered into the database (PPD eCRF):

- Any modification to DTG or ABC/DTG/3TC dose or formulation at the current visit or since the last visit.
- Weight
- Plasma HIV-1 RNA viral load (as collected per local SOC)
- Pregnancy status (urine or serum pregnancy test results)
- Primary reason for study withdrawal: Subjects are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the eCRF. The Study Discontinuation eCRF Form must also be completed. Every effort should be made by the investigator to follow-up patients who withdraw from the study.
- Any SAE
- Any AE leading to treatment discontinuation

The following assessment are to be performed per local SOC at the withdrawal visit (if different from a regular visit) and **should be recorded in the investigator's patient records; these results will not be entered into the database (PPD eCRF)**: Blood sample for laboratory assessments per investigator's judgment for the follow-up of a clinically significant abnormality; any changes in concomitant medications and background ART; and any assessments as per SOC according to local practices and guidelines (lipid profiles, CD4+, etc.).

7.6. Safety

At every study visit, the subjects will be asked to provide details of any AEs that have occurred. All SAEs, and all AEs that lead to IP discontinuation, will be documented and reported by the investigator. Additional information regarding detecting, documenting and reporting AEs and SAEs is available in Section 7.6.1.

The Sponsor recommends local laboratory assessment of hematology and clinical chemistry parameters as per local practice and regulatory guidelines when the investigator feels there is cause for these assessments. The results of these tests will not be collected in the eCRF unless the result(s) are considered to be an SAE by the investigator.

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. All SAEs, and all AEs leading to treatment discontinuation, will be reported.

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

- All SAEs, and all AEs leading to treatment discontinuation, will be recorded from the time a subject provides consent to participate in the study, up to and including any Follow-up Visit.
- All SAEs and all clinical or laboratory events leading to discontinuation of IP will be recorded and reported to PPD within 24 hours, as indicated in Appendix 7 Section 12.7.3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects (after the subject has exited the study). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to IP or study participation, the investigator must promptly notify PPD.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to PPD are provided in Appendix 7.

7.6.1.2. Follow-up of SAEs and AEs leading to discontinuation of IP

After the initial event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs or any AEs leading to discontinuation of IP (including events meeting liver stopping criteria, as defined in Section 5.4.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4.2).

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

The events or outcomes listed in the Centers for Disease Control and Prevention (CDC) Classification System for HIV-1 Infections (Appendix 9 Section 12.8), as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes, are not reported to PPD as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition Appendix 7, or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with IP
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If either of the above conditions is met then record the Disease Related Event (DRE) on the SAE page or the AE leading to IP discontinuation eCRF page, as applicable, and report promptly [see Section 12.7.5] to PPD.

7.6.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to PPD of SAEs related to study treatment (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. PPD must notify ViiV Healthcare of any SAEs within 24 hours of learning of the event or the next business day if notified during a weekend or public holiday.

ViiV Healthcare has a legal responsibility to ensure that both the local regulatory authority and other regulatory agencies are notified about the safety of a product under clinical investigation. ViiV Healthcare working with PPD will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators. Investigators must comply with any additional country specific reporting requirements.

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

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK on behalf of

ViiV Healthcare will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.6.2. Pregnancy

7.6.2.1. Pregnancy Testing

Female study subjects of reproductive potential are defined as girls who have reached menarche and have not undergone a sterilization procedure (hysterectomy or bilateral oophorectomy). Appropriate site personnel should determine the menarche status of female study subjects who reach the age of reproductive potential during study and who are suspected of having initiated sexual activity. Female study subjects who reach reproductive potential during the study and who are sexually active or who are considering becoming sexually active should be provided with contraception counselling during their participation in the study. Counselling should cover at minimum: the potential risks associated with pregnancy (see Section 4.6 for specific risks) during the trial; the uncertainty of long-term effects of ART on infant outcome; and avoiding pregnancy, safer sexual practices and the proper use of the subjects' chosen contraceptive methods.

All study subjects must agree to NOT participate in a conception process (e.g. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization).

Female subjects who are of childbearing potential and who are engaging in sexual activity that could lead to pregnancy, must use one of the acceptable birth control options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Appendix 3 Section 12.3.1 until the last dose of IP and completion of the Follow-up Visit (4 weeks after the last dose of IP). Condoms are recommended in addition, because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

All female subjects of childbearing potential must have a negative pregnancy test at Screening and Day 1 to be eligible for enrollment and will be tested again at the time of study withdrawal. Pregnancy testing may also be conducted any time during the trial when pregnancy is suspected. Additionally, a pregnancy test should also be performed prior to IP re-administration, when dosing is disrupted for more than 7 days. Pregnancy tests must be performed on urine as per local SOC.

A pregnancy (intrauterine), regardless of termination status of pregnancy, will result in subject withdrawal.

7.6.2.2. Pregnancy Reporting

Details of all pregnancies in female subjects will be collected over the period starting at Screening and ending at the final or Follow-up visit. If a pregnancy is reported then the investigator should inform PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3 (Section 12.3.2).

GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of

ARV products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

7.6.3. Physical Exams

Physical exams should be conducted as part of normal routine clinical care per local SOC but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g. in the current medical conditions or AE logs). AEs are recorded if they are serious or cause withdrawal from treatment.

7.6.4. Vital Signs

Vital signs should be measured per local SOC practices and may include height, temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate.

A measure of weight must be included in these assessments and will be recorded in the eCRF.

7.6.5. Suicidal Risk Monitoring

Subjects with HIV infection occasionally may present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with INSTIs, including DTG. Therefore, it may be appropriate, depending on the age of the subject, to monitor for suicidality before and during treatment.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior. Subjects presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the IP may be required.

7.6.5.1. Possible Suicidality Related Adverse Events

If any patient experiences a possible suicidality-related adverse event (PSRAE) while participating in this study that is considered by the investigator to meet definitions for seriousness (Appendix 7, Section 12.7.2), the investigator will collect information using the PSRAE eCRF form in addition to the SAE eCRF form. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to PPD within 1 week of the investigator diagnosing a possible suicidality-related AE, if the PSRAE is a SAE or if the PSRAE leads to treatment discontinuation. In the case of SAE, the SAE eCRF should be completed and submitted within 24 hours of diagnosing a possible suicidality related SAE.

8. DATA MANAGEMENT

For this study, minimal patient data (i.e., demographics, SAEs and any AE leading to withdrawal/discontinuation of DTG) will be entered into eCRFs, transmitted electronically to PPD and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

SAE terms will be coded using the Medical Dictionary for Regulatory Activities. In all cases, patient initials will not be collected or transmitted to PPD according to PPD policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This is an open-label, rollover study. No formal hypothesis testing will be performed. The objectives of this study will be supported through evaluation of SAEs, which will be categorized according to the DAIDS Table for grading pediatric AEs (Appendix 10, Section 12.10). Data will provide only descriptive information on safety and tolerability.

9.2. Sample Size Considerations

Based on the design of the parent studies, a maximum of 300 pediatric subjects with HIV could enroll in this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The safety population will comprise all subjects who have received at least one dose of IP once enrolled in this study. This population will be used for analyses of safety data.

9.3.2. Interim Analysis

No interim analysis is planned, however, data may be pulled periodically to support registrations and/or safety analyses updates.

9.4. Key Elements of Analysis Plan

SAEs will be summarized and categorized by the DAIDS toxicity scale (Appendix 10, Section 12.10). The SAE analyses will take place upon closure of the protocol; however, data cuts and analyses may be conducted as necessary in order to support regulatory submissions and/or publications.

All summaries will be presented by the parent study. Descriptive listings will be provided.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted by PPD on www.clinicaltrials.gov before enrollment of subjects begins.

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

Prior to initiation of a site, PPD on behalf of ViiV Healthcare, will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

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

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- ViiV Healthcare/GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Written informed consent for study participation will be obtained before any study-specific procedures are performed. Since the Screening visit overlaps with the Week 180 visit in P1093 or the Week 36 visit in P2019 (or later visits) of the parent studies, the informed consent process will be conducted before any study assessment activities begin.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures

to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

It is generally expected that only one parent or legal guardian will provide informed consent for the child's participation in this study. However, parental consenting requirements at each site will depend on the IRB/IEC risk determination.

Should the parent or legal guardian of an enrolled child die or no longer be available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. Study sites should establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/IEC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

10.2.1. Children in care

DAIDS is a sponsor of the parent studies. As per DAIDS policy, children in care (i.e children who are wards of State or any other agency, institution or entity) may be enrolled in the parent studies. Under ViiV Healthcare sponsorship, the recruitment of children in care is only permitted with Chief Medical Officer (CMO) approval. As post study drug access and continuity of care for all children and adolescents in the parent studies is provided through 205858 (ViiV Healthcare sponsored study), the ViiV CMO has approved the transition of eligible children in care enrolled in the parent studies into the 205858 study. Transition of eligible children in care will ensure continuity of care and access to IP until age appropriate formulations receive local regulatory approval and are commercially available or are available from another source (e.g. government programs, aid programs, assistance programs), or the subject no longer derives benefit from IP or meets a protocol defined reason for discontinuation.

Sites must establish and maintain written procedures describing local standards for identifying who may serve as legal guardian for a clinical research subject and how guardianship will be recognized within the context of available IRB/IEC guidance, local law, regulation and/or government policy. Evidence of guardianship should be documented at study entry and during the study if a change in guardianship occurs.

- If a subject is a child in care (ward of state or any other agency, institution or entity) at the time of screening, the site investigator must notify the Study Medical Monitor prior to enrollment. Documentation of appropriate guardianship (within the context of available IRB/EC guidance, local law, regulation and/or government policy) must be provided and confirmed by the Study Medical Monitor prior to enrollment.

- If a change in guardianship occurs and the subject becomes a child in care (ward of state or any other agency, institution or entity) during the study, the site investigator must notify the Study Medical Monitor immediately. The ViiV CMO will review cases and determine if subjects may continue to participate in the study.

- Child in care status at the time of enrollment will be entered into the eCRF for all subjects enrolled in the study. Changes in guardianship resulting in a subject becoming a child in care during study conduct will also be entered into the eCRF.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and PPD procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ViiV Healthcare/GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.
- Data reported in the eCRFs that are transcribed from source documents (i.e. documentation from the parent study) 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.

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Participation of a subject in study 205858 will end when an age appropriate formulation of IP becomes available to the subject, unless the study is terminated early. Unless terminated early, this study will be considered completed after the last subject completes the last study-related clinic visit or assessment.

- Upon completion or premature discontinuation of the study, PPD will remotely conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ViiV Healthcare/GSK Standard Operating Procedures, as appropriate.
- ViiV Healthcare/GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If ViiV Healthcare/GSK or its designee determines such action is needed, ViiV Healthcare/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV Healthcare/GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, ViiV Healthcare/GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV Healthcare/GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, including the eCRFs (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a ViiV Healthcare/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- ViiV Healthcare/GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, ViiV Healthcare/GSK standards/procedures, and/or institutional requirements, as appropriate.
- The investigator must notify ViiV Healthcare/GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.
- eCRFs (including queries and audit trails) will be retained by ViiV Healthcare/GSK, and copies will be sent to the investigator to maintain as the investigator copy

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a study site or other mutually-agreeable location.

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

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

3TC	lamivudine
ABC	abacavir
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease - 2019
CMO	Chief Medical Officer
eCRF	Electronic case report form
c/mL	Copies per millilitre
DAIDS	Division of AIDS (United States)
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRV	darunavir
DT	Dispersible tablet
DTG	Tivicay (dolutegravir)
EFV	efavirenz
EMA	European Medicines Agency
ETR	etravirine
EU	European Union
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPV	fosamprenavir
FTC	emtricitabine
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HLA	Human leukocyte antigen

HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials (Network)
IgM	Immunoglobulin M
INR	International Normalized Ratio
INSTI	Integrase strand transfer inhibitor
IP	Investigational product
IRB	Institutional Review Board
kg	Kilogram
LAR	Legally authorized representative
LOC	Local operating company
mg	Milligrams
mL	Millilitre
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PI	Principal investigator
PK	Pharmacokinetics
PMTCT	Prevention of mother-to-child transmission
PPD	Pharmaceutical Product Development
RNA	Ribonucleic acid
RTV	ritonavir
SAE	Serious Adverse Event
SJS	Stevens-Johnson Syndrome
SOC	Standard of Care
TB	Tuberculosis
TDF	tenofovir disoproxil fumarate
TEN	Toxic Epidermal Necrolysis
TPV	tipranavir
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States (of America)
VF	Virological Failure
VSLC	ViiV Healthcare Safety and Labelling Committee

Trademark Information

Trademarks of ViiV Healthcare
Tivicay
Tivicay PD
Triumeq

Trademarks not owned by ViiV Healthcare
None

12.2. Appendix 2 – Dosing Tables

The dosing tables provided below align to those used in the P1093, and P2019 parent studies.

As new data become available, subjects in this study may be able to switch to different DTG (and/or ABC and 3TC) doses (e.g. new doses to receive local licensure or doses recommended in local treatment guidelines, if updated) than outlined below. A change from the dosing approach used in the parent study must be discussed and agreed with the ViiV Medical Monitor.

If new dosing for either DTG or ABC/DTG/3TC is approved during the conduct of this study, subjects will be allowed to switch to these doses as allowed by local practice.

12.2.1. Tivicay DTG Film Coated Tablets

- The DTG 50 mg film coated tablet is approved for use in children weighing 20 kg and above.

- Subjects using the DTG 30 mg dispersible tablet dose may switch to the DTG 50 mg film coated tablet as appropriate (i.e., Investigator determines the participant is able to swallow the tablet and use is appropriate).

12.2.2. DTG Dosing Table for subjects transitioning from parent study P1093

Table R – Dispersible Tablets **– with maximum dose of 30 mg***

Age	Weight Band (kg)	Dose (mg)	Dose (mg/kg)	
			low weight	high weight
≥ 4 weeks to < 6 months of age	3 - <6	5	1.67	0.83
	6 - <10	10	1.67	1.00
≥ 6 months of age	3- < 6	10	3.33	1.67
	6- <10	15	2.50	1.50
	10 - <14	20	2.00	1.43
	14 - <20	25	1.79	1.25
	≥20	30	1.50	

***Subjects who reach the 30 mg dose may be able to switch to the film coated 50 mg tablet**.

12.2.3. ABC/DTG/3TC Dosing table for subjects transitioning from parent study P2019

ABC/DTG/3TC tablets (60 mg/5 mg/30 mg dispersible tablets or 600 mg/50 mg/300 mg immediate release [Triumeq] tablets) will be taken once daily, generally with or without food, at doses specified below:

Weight Band		Study Drug Formulation (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	3 dispersible tablets (180/15/90 mg)
#2	10 to less than 14 kg	4 dispersible tablets (240/20/120 mg)
#3	14 to less than 20 kg	5 dispersible tablets (300/25/150 mg)
#4	20 to less than 25 kg	6 dispersible tablets (360/30/180 mg)
#5	25 kg or greater	1 immediate release tablet (600/50/300 mg)

12.3. Appendix 3 – Pregnancy

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

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

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

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

12.3.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an SAE or an AEs leading to discontinuation of IP where applicable.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.7.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

12.4. Appendix 4 – Liver Safety – Study Treatment Restart Guidelines

If a causal relationship between the liver event and IP cannot be ruled out, then IP must be permanently discontinued and the subject not rechallenged.

12.4.1. Drug Restart Following Transient Resolving Liver Events Not Related to Study Drug

Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT<3xULN) where:

- Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury.
- If restart of ABC/DTG/3TC is being considered, then the subject must be HLA-B*5701 negative (even in countries where HLA-B*5701 screening is not considered standard of care).
- The subject is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from the ViiV Healthcare Safety and Labelling Committee (VSLC) and Ethics Committee or Institutional Review Board for the drug restart has been obtained.
- The subject has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death.
- The subject has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file.
- Following drug restart, it is recommended that the Subject return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

12.5. Appendix 5 – Liver Safety – Checklist for Drug Restart Approval or Refusal

"Drug restart" after discontinuation of Study Drug due to Liver Stopping Criteria (as defined in the protocol), can only be approved by the ViiV Safety and Labelling Committee (VSLC) for **transient, defined non-drug-induced liver injury with no evidence of:**

- immunoallergic injury/HLA association with injury
- drug-induced liver injury
- alcoholic hepatitis

Investigators MUST:

1. Hold study drug while labs and evaluations are completed to assess diagnosis, and not restart until "Drug restart" has been approved by the VSLC.
2. Complete the table below and submit to the VSLC. The Liver Event case report form should already have been submitted to PPD, along with liver imaging and/or liver biopsy case report forms and/or SAE case report form where applicable. Where restart of ABC/DTG/3TC is being considered, provide documentation verifying HLA-B*5701 status.

Subject Number:	**Yes**	**No**
Have liver chemistries improve to within 1.5x baseline and ALT<3xULN?		
Was subject's HIV infection stable or improving on Study Drug?		
Were any of the **following high-risk factors** included in the initial liver injury event? **(Do not restart if 'Yes' for any one of the following high-risk factors)**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (aspartate aminotransferase>ALT, typically <10xULN)		
• Study Drug (other than ABC) has an HLA genetic marker associated with liver injury		
For restart of TRIUMEQ, or any other abacavir- containing Study Drug, the subject MUST be HLA-B*5701 negative[1] Specify HLA-B*5701 status[2]:		

1. In countries/regions where HLA-B*5701 pre-therapy screening is not considered standard of care, subjects stopping abacavir- containing study drug due to Liver Stopping Criteria MUST be tested and found to be negative for the HLA-B*5701 allele before abacavir-containing Study Drug can be re-started.
2. If study drug does not contain ABC then record HLA-B*5701 status as "not applicable"

12.6. Appendix 6 – Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (See Appendix 10, Section 12.10). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 12.7, Appendix 7.

Study drug may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimise the risk of development of resistance.

No toxicity-related dose reductions of study drugs will be allowed. Study drugs should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of study drugs or temporary interruption of one but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on subject management and study drug interruptions based on the severity of the AE for specific toxicities. All changes in study drug must be accurately recorded in the subject's eCRF.

Note: For subjects receiving an ABC-containing product as part of the background regimen, in the event of a discontinuation of ABC for any reason, reinitiation of this drug should be undertaken with caution. The investigator should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product, evaluate for the possibility of a clinically suspected HSR, and initiate subject management as outlined in the Local Country Prescribing Information, regardless of a subject's HLA-B*5701 status. Screening for the presence of HLA-B*5701 is recommended prior to reinitiating treatment with ABC-containing products in subjects of unknown HLA-B*5701 status who have previously tolerated ABC.

For general guidelines on the management of specific toxicities (including liver chemistry stopping and follow up criteria, restarting study drug, decline in renal function, allergic reaction, rash, hypertriglyceridaemia/hypercholesterolaemia and creatine phosphokinase (CPK) elevation) that are considered to be related or possibly related to study treatment see Section 12.6.1. Specific Toxicities/Adverse Event Management.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment at the discretion of the investigator. Subjects who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Subjects who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by study treatment, dosing may continue after discussion with the Medical Monitor.

Subjects who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the study drugs should have study treatment withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study treatment may be restarted.

Should the same Grade 3 AE recur within 28 days in the same subject, study treatment should be permanently discontinued and the subject withdrawn from study. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and have withdrawal study evaluations completed. A Follow-up visit should be performed 4 weeks after the last dose of study drugs.

Subjects with asymptomatic Grade 3 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue study drug if the investigator has compelling evidence that the toxicity is not related to study treatment.

Exceptions are noted for lipid abnormalities in Section 12.6.1.6 and rash in Section 12.6.1.5 respectively.

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should have study treatment discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the study drugs, dosing may continue after discussion with and assent from the Medical Monitor. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

Subjects with asymptomatic Grade 4 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to study treatment. Exceptions are noted for lipid abnormalities in Section 12.6.1.6. An in-clinic Follow-up visit will be conducted approximately 4 weeks after the last dose of IP for subjects with ongoing AEs, and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit.

12.6.1. Specific Toxicities/Adverse Event Management

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

Subjects who permanently discontinue study treatment for reasons of toxicity should be followed weekly until resolution of the AE and be encouraged to complete the withdrawal and follow-up study evaluations as noted in Appendix 7, Section 12.7.3.

12.6.1.1. Decline in Renal Function

Refer to Section 5.4.3 Management of Renal Toxicity.

12.6.1.2. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 5.4.4 and Appendix 4 Section 12.4.

12.6.1.3. Restarting Study Drug

Refer to Appendix 4 Section 12.4 for details on drug restart following transient resolving liver events not related to study treatment.

12.6.1.4. Allergic reaction

Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the investigator. The subject should be advised to contact the investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study drug should permanently discontinue study treatment and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information.

12.6.1.5. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within 2 to 3 weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB.

Subjects with an isolated Grade 1 rash may continue study drug at the investigator's discretion. The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Subjects may continue study drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Subjects should permanently discontinue study drug [and all other concurrent medication(s) suspected in the investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the etiology of the rash has been definitively diagnosed as NOT attributable to study drug (see below), and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g. viral infection) or start of concomitant medication.

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, Appendix 10, Section 12.10).

However, if the etiology of the rash has been definitively diagnosed as being unrelated to IP and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed, and documentation of the diagnosis provided. In this situation, the study drug should be continued. Subjects receiving ABC should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information.

12.6.1.6. Hypertriglyceridemia/Hypercholesterolemia

If monitored per local SOC, the Sponsor recommends that samples for lipid measurements be obtained in a fasted state every 12 weeks. Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study drug.

12.6.1.7. Co-infection with TB

Subjects who are already enrolled and are on therapy who become exposed to tuberculosis (TB), and subsequently require an anti-TB treatment that includes the use of rifampin are permitted to continue in the study if their ART options are compatible with co-administration of rifampin. Management of these subjects is as follows:

- When administration of the rifampin-containing anti-TB treatment begins, subjects will increase their DTG dose from once daily to twice daily (dose is

based on weight). DTG study treatment duration continues to be administered twice daily while subject is on the rifampin containing anti-TB therapy.

- It is estimated the subject will be on anti-TB treatment for approximately 24 weeks. Approximately two weeks after discontinuation of the rifampin containing anti-TB therapy, the subject's DTG dose will revert back to once daily administration unless on EFV, ETR, NVP, or TPV/RTV.

Subjects who roll-over from the parent study during the course of rifampicin containing therapy should continue their DTG dose twice daily. Approximately two weeks after discontinuation of the rifampin containing anti-TB therapy, the subject's DTG dose will revert back to once daily administration unless on EFV, fosamprenavir (FPV)/RTV, or TPV/RTV.

For subjects from the P2019 parent study who are taking FDC ABC/DTG/3TC, it is generally expected that the frequency of DTG dosing will be increased from once daily to twice daily, using a single agent formulation of DTG for the second daily dose; doses and formulations to be provided are shown in Table 5. Approximately two weeks after discontinuation of rifampin treatment, the study drug regimen corresponding to the child's current weight should be resumed.

Table 7 Second Daily Dose of DTG for Children in P2019 Who Require Rifampin-Containing TB Treatment

Weight Band		Second Daily Dose of DTG
#1	6 to less than 10 kg	DTG 15 mg (three 5 mg dispersible tablets)
#2	10 to less than 14 kg	DTG 20 mg (four 5 mg dispersible tablets)
#3	14 to less than 20 kg	DTG 25 mg (five 5 mg dispersible tablets)
#4	20 to less than 25 kg	DTG 30 mg (six 5 mg dispersible tablets) **OR** DTG 50 mg (one film coated tablet)
#5	25 kg or greater	DTG 50 mg (one film coated tablet)

12.6.1.8. Subjects Co-infected with Hepatitis B Virus (HBV)

Investigators should consult current treatment guidelines (e.g. [DHHSa, 2019; DHHSb, 2019]) when considering choice of NRTIs for subjects with chronic HBV infection (HBsAg positive OR anti-HBc positive with HBV DNA present).

In addition, clinical trial and marketed use of 3TC, FTC and TDF have shown that some subjects with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, FTC or TDF, which may have more severe consequences in subjects with decompensated liver disease. Subjects with HBV co-infection should be advised against self-discontinuation of any medications with anti-HBV activity. If 3TC, FTC or TDF is discontinued in subjects co-infected with HBV, periodic monitoring of both liver chemistry tests and markers of HBV replication should be performed.

Entecavir and telbivudine are permitted, in appropriate clinical situations, for treatment of HBV (e.g. prior intolerance or viral resistance to TDF, viral resistance to 3TC/FTC) after discussion and agreement between the investigator and the medical monitor.

12.6.1.9. ABC Hypersensitivity

Both ABC and DTG are associated with a risk for a hypersensitivity reaction and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Clinically it is not possible to determine whether a hypersensitivity reaction with ABC/DTG/3TC fixed dose combination is caused by ABC or DTG. Hypersensitivity reactions have been observed more commonly with ABC, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately. More detailed clinical descriptions of these reactions are included in the ABC/DTG/3TC Investigator Brochure and Local Prescribing Information.

The risk for ABC hypersensitivity reactions to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, ABC hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of HLA-B*5701 and subsequently avoiding ABC in HLA-B*5701 positive patients, significantly reduced the incidence of clinically suspected ABC hypersensitivity reactions from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$) [Mallal, 2008]. In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were HLA-B*5701 negative and who received ABC developed a clinically suspected ABC hypersensitivity reaction, respectively [Post, 2010, Squires, 2010].

The following should be adhered to in the management of subjects presenting with signs and symptoms suggesting a possible hypersensitivity reaction:

- In any subject treated with ABC/DTG/3TC, the clinical diagnosis of a suspected hypersensitivity reaction must remain the basis of clinical decision making.
- ABC/DTG/3TC must be stopped without delay, even in the absence of the HLA-B*5701 allele, if a hypersensitivity reaction is suspected. Delay in stopping treatment with ABC/DTG/3TC after the onset of hypersensitivity may result in a life-threatening reaction. Clinical status including liver aminotransferases and bilirubin should be monitored.
- Subjects who have experienced a hypersensitivity reaction should be instructed to return their remaining ABC/DTG/3TC tablets to the site, in order to avoid restarting ABC.
- After stopping treatment with ABC/DTG/3TC for reasons of a suspected hypersensitivity reaction, ABC/DTG/3TC or any other medicinal product containing ABC or DTG must never be re-initiated.
- Restarting ABC-containing products following a suspected ABC hypersensitivity reaction can result in a prompt return of symptoms within hours and may include life-threatening hypotension and death.

- If a hypersensitivity reaction is ruled out, Subjects may restart ABC/DTG/3TC. Rarely, patients who have stopped ABC for reasons other than symptoms of a hypersensitivity reaction have also experienced life-threatening reactions within hours of re- initiating ABC therapy. Subjects must be made aware that a hypersensitivity reaction can occur with reintroduction of ABC/DTG/3TC or any other medicinal product containing ABC and that reintroduction of ABC/DTG/3TC or any other medicinal product containing ABC should be undertaken only if medical care can be readily accessed.

12.6.1.9.1. Reporting of ABC Hypersensitivity Reactions

If a clinically suspected case of a hypersensitivity reaction to ABC meets one of the ICH E2A (ICH E2A, 1994) definitions of seriousness listed in Section 12.7.2 then, in addition to reporting the case as a serious adverse event, the ABC hypersensitivity reaction case report form should also be completed within one week of the onset of the hypersensitivity reaction and sent to the Sponsor.

In the event of a discontinuation of ABC/DTG/3TC for any reason, re-initiation of this drug should be undertaken with caution. The investigator must obtain a complete history of the events surrounding the discontinuation of ABC/DTG/3TC, evaluate for the possibility of a clinically suspected hypersensitivity reaction, and initiate subject management as outlined in Section 12.5 regardless of a subject's HLA-B*5701 status.

12.7. Appendix 7 – Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.7.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

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

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.7.2. Definition of Serious Adverse Events

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury and impaired liver function defined as:

- ALT >3xULN and total bilirubin >2xULN (>35% direct bilirubin)

12.7.3. Recording of SAEs and AEs leading to discontinuation of IP

AEs and SAE Recording:

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

12.7.4. Evaluating AEs and SAEs

Assessment of Intensity

Every AE and SAE reported during the trial should be evaluated by the investigator and graded in the eCRF according to the DAIDS toxicity scales (see Appendix 10, Section 12.10).

Where a DAIDS toxicity scale is not available for a particular event or parameter, then

the investigator will instead make an assessment of intensity using one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

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

Follow-up of SAEs and AEs leading to discontinuation of IP

- The investigator is obligated to perform or arrange for the conduct of supplemental

measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the SAE or AE leading to discontinuation of IP.

- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK 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 event data to GSK within the designated reporting time frames.

12.7.5. Reporting of SAEs and AEs leading to discontinuation of IP to GSK/ViiV Healthcare/PPD

Reporting to PPD via electronic data collection tool

- Primary mechanism for reporting SAEs and AEs leading to discontinuation of IP to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE or AEs leading to discontinuation of IP CRF and fax it to the PPD Medical Monitor
- Site will enter the event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 or AEs leading to discontinuation of IP from a study subject or receives updated data on such a previously reported event after the electronic data collection tool has been taken off-line, the site can report this information on a paper CRF or to the PPD Medical Monitor by telephone.
- Contacts for event receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.7.6. Reporting COVID-19 Related SAEs and AEs Leading to Treatment Discontinuation

Refer to Section 12.8 (Appendix 8 COVID-19 Pandemic and Study Guidance) for guidance on the reporting of COVID-19 specific SAEs and AEs leading to treatment discontinuation.

12.8. Appendix 8 – COVID-19 Pandemic and Study Guidance

12.8.1. COVID -19 Experimental Agents

As vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that HIV-1 RNA collection occur 2-4 weeks from COVID vaccination.

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

12.8.2. COVID-19 Specific Data Capture

12.8.2.1. Capturing COVID-19 Specific Protocol Deviations

Please contact your Study CRA if protocol deviations are anticipated or occur as a result of COVID-19.

12.8.2.2. Capturing COVID-19 Specific SAEs and AEs Leading to Treatment Discontinuation

For this study, only SAEs and AEs leading to treatment discontinuation are captured in the eCRF.

It is important for the study team to describe COVID-19 related Serious Adverse Events, or Adverse Events leading to treatment discontinuation, and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs leading to treatment discontinuation should be submitted following usual study procedures and timelines.
2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any SAEs or AEs leading to treatment discontinuation.
3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released 20 Mar 2020, represents a time point for standardized collection. The definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events leading to treatment discontinuation related to COVID-19 infection, investigators should use the following Verbatim terms:
    a. Suspected COVID-19 infection; or
    b. Probable COVID-19 infection; or
    c. Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.
5. A new COVID-19 infection Case Report Form has been added to the eCRF to collect additional details about the reported COVID-19 SAE or AE leading to treatment discontinuation. It is important to collect the correct information from each participant reporting a COVID-19 SAE or AE leading to treatment discontinuation. Therefore, please use the CRF templates to collect this information.

WHO Case Definition - March 20, 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))**:**

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;
   OR
B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;
   OR
C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).
   OR
B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A Covid-19 contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;

3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

12.9. Appendix 9 – CDC and WHO Classification Systems for HIV-1 Infections

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm

World Health Organization (WHO). WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children. Available at: https://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

12.10. Appendix 10 – DAIDS Toxicity Scales

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 [July 2017]. Available from:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Note: 205858 Rollover Study protocol specific guidance - For the grading of creatinine and creatinine clearance, please refer to Section 5.4.3 and use the absolute value for creatinine and creatinine clearance in the DAIDS tables when determining creatinine and creatinine clearance DAIDS severity band.

12.11. Appendix 11 – Country Specific Requirements

No country-specific requirements exist.

12.12. Appendix 12 – Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Detailed summary of changes for Protocol Amendments 1, 2, and 3 are contained within Section 12.11 (Appendix 11) of Protocol Amendment 3.

ViiV Healthcare/ GlaxoSmithKline Document Number	**Date**	**Version**
2016N282439_00	23-AUG-2016	Original
2016N282439_01	26-SEP-2016	Amendment No. 1
Patients enrolling at sites in some countries without approval for pediatric dosing of dolutegravir need to be enrolled in a Phase IIIB study. Therefore, the development stage of the protocol has been changed from a Phase IV to a Phase IIIB study in order to account for these global regulatory requirements. In addition, we have made minor changes to the exclusion criteria in response to feedback from the FDA.		
2016N282439_02	29-JUN-2018	Amendment No. 2
The potential risk for neural tube defects has been added to the risk:benefit section. Dosing tables were updated to align to the parent study (P1093). Background information on the parent study (P1093) was updated, including sample size. Reference to collection of PK samples, which were included in error, have been removed. Other clarifying text and correction of typographical errors have been addressed.		
2016N282439_03	27-JUN-2019	Amendment No. 3
Amendment 03 incorporates the transition of subjects from a second parent study, P2019, into this open label rollover study. The study will provide access to age appropriate formulations of dolutegravir (DTG), either as Tivicay or as fixed dose combination (FDC) abacavir/dolutegravir/lamivudine (ABC/DTG/3TC), to eligible subjects who have completed the P1093 Study or P2019 parent studies. Both parent studies P1093 and P2019 are sponsored by the Division of Acquired Immunodeficiency Syndrome (DAIDS) the National Institute of Allergy and Infectious Disease (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and implemented by the International Maternal Paediatric Adolescent AIDS Clinical Trial Network (IMPAACT). P2019 is a Phase I/II study which examines the pharmacokinetics, safety, and tolerability of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) dispersible and immediate release tablets in HIV-1-infected children less than 12 years of age. ViiV Healthcare plans to seek licensure of ABC/DTG/3TC for pediatric use in countries		

where parent study P2019 is conducted. In countries where ABC/DTG/3TC is not locally available in the age appropriate formulation at the time of subject completion of the P2019 study, and where the subject is deriving benefit from ABC/DTG/3TC, ViiV Healthcare will provide ABC/DTG/3TC to subjects within this ViiV sponsored study. Criteria for inclusion and management of subjects from P2019 were embedded throughout the protocol. Liver chemistry stopping criteria, required use of contraception, and criteria for IP restart were updated to reflect ViiV Healthcare guidance for DTG and DTG containing products in ViiV sponsored studies.		
2016N282439_04	10-DEC-2020	Amendment No. 4
To more closely align with subject management in the IMPAACT P1093 and P2019 parent protocols, eligibility criteria were clarified. Virologic failure due to non-adherence, intercurrent illness or other factors not associated with the study drug, did not automatically lead to permanent discontinuation of study drug and participant withdrawal from the DAIDS sponsored parent studies (IMPAACT P1093 and P2019). Therefore, subjects may have experienced confirmed virologic failure with subsequent virologic control and evidence of ongoing clinical benefit from the study drug while in the parent studies. Eligibility for participation in the 205858 study was clarified throughout the protocol with the removal of references to 'no evidence of virologic failure in the parent studies' and the addition of inclusion criterion #3, which requires confirmation of supporting evidence of the subject's continued benefit from use of the Investigational Product during participation in the parent study. Evidence of virologic control at the time of completion of the parent study (inclusion criterion #2, confirmed by viral load) is also required. In addition, exclusion criterion #1 was added to exclude participants who have had confirmed virologic failure with evidence of resistance to either a) DTG in the P1093 parent study or b) ABC, DTG or 3TC (with the exception of M184V) in the P2019 parent study.		

Section # and Name	Description of Change	Brief Rationale
Title Page	Modified title page formatting. (No change to study specific information).	Formatting was updated to align with current revised ViiV Healthcare Clinical Protocol Master Template title page
Protocol Amendment Summary of Changes	The protocol amendment revision chronology section was updated to provide rationale and changes for Protocol Amendment 04. Rationale for prior Protocol Amendments 01, 02 and 03 were moved to Section 12.13 (Appendix 13)	The Protocol Amendment Summary of Changes section was modified to align with the current ViiV Healthcare Clinical Protocol Master Template and process for documentation of protocol amendment changes. Revised text from Protocol Amendments 01, 02 and 03 can be found in Section 12.11 (Appendix 11, Protocol Changes) of prior Protocol Amendment 03.
Throughout	Added the marketed name the for dolutegravir (DTG) dispersible tablet in the United States - 'Tivicay PD'.	In the United States, the DTG dispersible tablet was approved and is marketed as Tivicay PD™. Reference to the approval and marketed name (Tivicay PD™) was incorporated.
Throughout	Where DTG was referenced as 'Tivicay', 'Tivicay' was replaced with 'single entity DTG' or 'DTG'.	'Single entity DTG' or 'DTG' was used to more inclusively references both Tivicay and Tivicay PD marketed names.
4.6.1 Risk Assessment for DTG	Incorporated updated neural tube defect data from the birth outcomes surveillance study conducted in Botswana.	Aligned with current DTG Investigator's Brochure.
4.6.1 Risk Assessment for DTG 4.6.2 Risk Assessment for ABC/DTG/3TC	Theoretical risk of serious drug interaction with fampridine was incorporated.	Aligned with current DTG Investigator's Brochure.
4.6.2 Risk Assessment for ABC/DTG/3TC	Updated to note ABC/DTG/3TC FDC should not be used in participants with creatinine clearance of less than 30 mL/min because, whilst no dosage adjustment of DTG or ABC is necessary in patients with renal impairment, dose reduction is required for the 3TC component.	Aligned with current DTG Investigator's Brochure.
4.6.3 Benefit Assessment	Updated safety and efficacy information for DTG pediatric P1093 and Odyssey studies.	Updated to align with current available data.
5.1 Inclusion Criteria (Inclusion Criterion 1, Duration in parent	Removed sub bullet which notes that subjects with evidence of virologic failure in either parent study must have eligibility	For clarity, a third separate inclusion criterion was added requiring evidence of continued benefit from IP during the subject's participation in the parent

studies)	for this rollover study discussed and agreed with the ViiV Healthcare Medical Monitor.	study (P1093 or P2019). Investigators will submit a clinical summary, verifying continued benefit, to the Study Medical Monitor for confirmation of criterion eligibility.
5.1 Inclusion Criteria (Inclusion Criterion 2, Virologic control at Screening)	Clarification added to note that a single HIV-1 RNA retest may be completed prior to the Day 1 visit to confirm virologic control criterion has been met.	A single HIV-1 RNA retest may be completed prior to Day 1 if needed. Virologic control must be confirmed prior to enrolment (Day 1 visit).
5.1 Inclusion Criteria (Inclusion Criterion 3, Evidence of clinical benefit in parent studies)	A third separate inclusion criterion was added requiring evidence of continued benefit from IP during the subject's participation in the parent study (P1093 or P2019). Investigators will submit a clinical summary, verifying continued benefit, to the Study Medical Monitor for confirmation of criterion eligibility.	Added to confirm evidence of clinical benefit from IP during participation in the parent studies.
5.2 Exclusion Criteria (Exclusion Criterion 1)	Exclusion criterion 1 was incorporated to exclude subjects who have had confirmed virologic failure with evidence of resistance to a) either DTG in the P1093 parent study or b) ABC, DTG or 3TC (with the exception of M184V) in the P2019 parent study.	Added to mitigate risk related to inclusion of subjects with prior resistance to DTG, ABC or 3TC and potential interference with continued benefit from IP.
5.2 Exclusion Criteria (Exclusion Criterion 3)	A timeframe of '30 days prior to study entry' was added to exclusion criterion 3: 'Known ≥Grade 3 laboratory toxicities within 30 days prior to study entry…'	Added for clarity.
5.4.3 Management of Renal Toxicity	Modified to incorporate instruction, based on change from baseline in DAIDS AE severity grading (Grades 1- 4), for serum creatinine and eGFR. Further clarification of how to determine creatinine and eGFR grade was also provided.	Modifications were made to clarify and simplify participant management. Stepwise instructions were incorporated, based on severity grade, for confirmatory testing and assessment and parameters for temporary holding or permanent discontinuation of study treatment. Further specific guidance on additional investigations that may be required and the need for consultation with the study Medical Monitor regarding further follow-up and management were incorporated.
6.1.1 Medical Devices 7.6.1.5 Medical Device Deficiencies 7.6.1.6 Time Period for Detecting Medical Device Deficiencies 7.6.1.7 Prompt	Added description of equivalent locally sourced medical devices for this study (dosing cup/syringe). Added the definition of a Device Deficiency and requirements for reporting.	Device Deficiency safety reporting requirements were incorporated into the protocol for alignment with the United States Food and Drug Administration (US FDA) 21 CFR 4 Subpart B (Regulation of Combination Products).

reporting of Medical Device Deficiencies to the Sponsor 12.8 Appendix 8 Reporting a Medical Device Deficiency		
6.5.2 DTG Dispersible Tablets	Updated to include current dispersion volumes for administration of the dispersible tablets, and instruction for a 5 mL water rinse following consumption of medication dose.	Updated to align with changes applied to parent protocol and Instructions for Use.
6.5.3 ABC/DTG/3TC Dispersible Tablets	Updated to include most current dispersion volumes for administration of the dispersible tablets, and instruction for a 15 mL water rinse following consumption of medication dose.	Updated to align with changes applied to parent protocol and Instructions for Use.
6.5.4 ABC/DTG/3TC Immediate Release (Triumeq™) Tablets	Updated to align with most current description of the product and storage conditions.	Updated to align with changes applied to parent protocol and Instructions for Use.
6.11.1 Permitted Medications	Instruction added for Investigators to consult with the Study Medical Monitor if any treatments for COVID-19 are planned for a study subject.	To ensure relevant drug interactions are considered and continuation of the subject in the study remains appropriate.
6.11.4 Additional considerations for ABC/DTG/3TC	Guidance pertaining to the use of riociguat was incorporated. Guidance added to note that the pediatric weight based once daily dose of the single entity DTG should be administered twice daily when ABC/DTG/3TC is co-administered with certain enzyme inducing drugs.	-Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving DTG/ABC/3TC FDC led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy participants. Riociguat dose may need to be reduced, consult the riociguat product labelling for dosing recommendations Aligned with current DTG Investigator's Brochure
7.6.2.2 Pregnancy Reporting 12.3.2 Collection of Pregnancy Information	Required timeframe for reporting subject pregnancy to the sponsor was changed from 'within 2 weeks' to 'within 24 hours'.	Alignment with updated ViiV Healthcare SOP and current ViiV Healthcare Clinical Protocol Master Template.
10.2.1 Children in care	Additional guidance for management and tracking of children in care (children who are wards of state or any other agency, institution or entity) has been added to Section 10.2.1 (Children in care).	Children in care are a vulnerable population. Close monitoring is required to confirm evidence of appropriate guardianship within the context of available IRB/IEC guidance, local law, regulation and/or government policy. All subjects enrolled in

		the study will be monitored for child in care status at screening and for any changes in status throughout study conduct.
12.2.2 (Appendix 2) Dosing Tables - DTG Dispersible Tablets	Dosing table section was simplified. Table 'R' was added.	Updated to align with current dosing instruction provided in the P1093 parent protocol.
12.6 (Appendix 6) Toxicity Management	Cross reference to Section 12.6.1 (Specific Toxicities/Adverse Event Management) was inserted.	Guidance for the management of specific toxicities (such as allergic reaction, rash, liver chemistry and others) are found in Section 12.6.1 of the protocol. Section 12.6.1 (Specific Toxicities/Adverse Event Management) should be used as the primary reference for management of specific conditions noted.
12.9 (Appendix 9) COVID-19 Pandemic and Study Guidance	Instructions for safety reporting and data capture of COVID-19 related SAEs or AEs leading to treatment discontinuation were incorporated.	It is important to describe COVID 19 related SAEs/AEs leading to treatment discontinuation and impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 21-Jun-2022 19:24:44 GMT+0000

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