Statistical Analysis Plan

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

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TITLE PAGE

Protocol Title:

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

Study Number: 205858

Compound Number: GSK1349572 and GSK2619619

Abbreviated Title: **The IMPAACT Studies P1093 and P2019 DTG Pediatric Roll-over trial**

Sponsor Name: [GlaxoSmithKline Research & Development Limited & ViiV Healthcare UK Limited]

Regulatory Agency Identifier Number(s)

Registry	**ID**
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	06 Oct 2023	Version 5 (06Jun2022)	Not Applicable	Original version

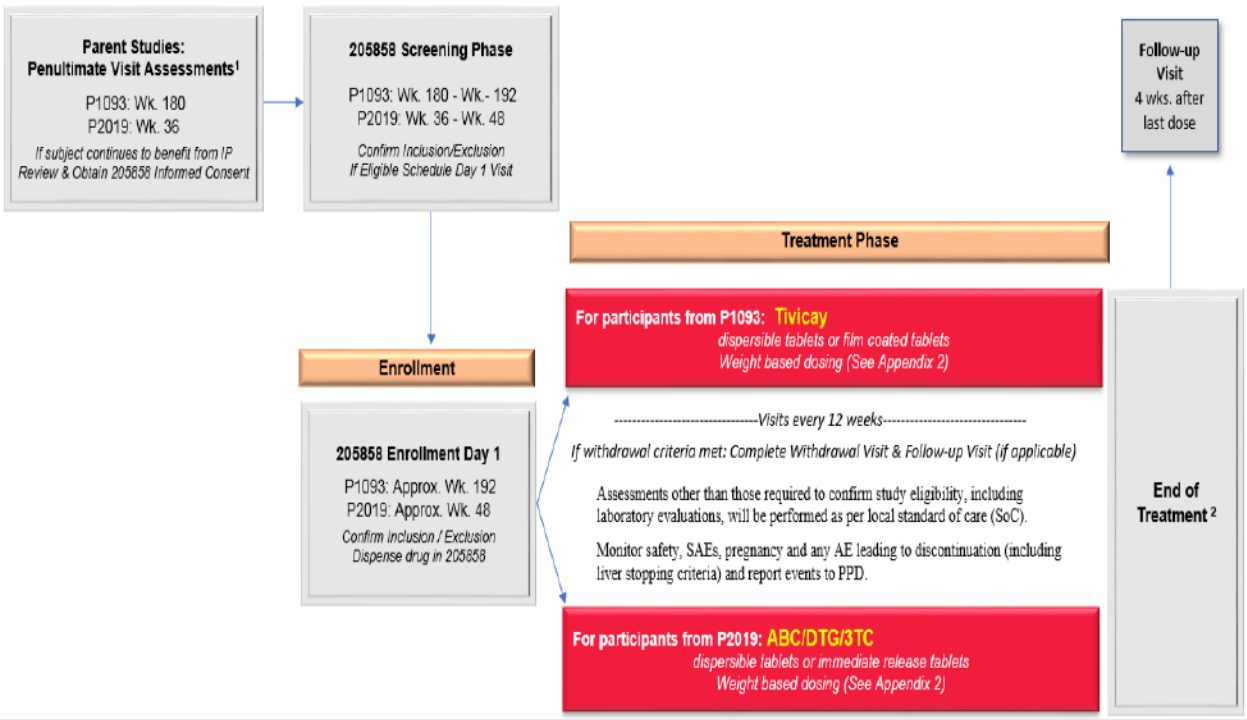
1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 205858. Details of the planned final analyses are provided.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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 IMPAACT P1093, or IMPAACT 2019 parent studies.	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).
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). 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). 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).To assess any serious adverse events (SAE) and any clinical or laboratory adverse events(AE) that lead to the discontinuation of IP (DTG, or ABC/DTG/3TC FDC)	

1.2. Study Design



1. See penultimate visit assessments in protocol 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.

The IMPAACT Studies P1093 and P2019 DTG paediatric Rollover study is a non-randomized, open-label, multi-center treatment, non-comparative study. The purpose of this study is to provide continued access to IP for eligible subjects who have completed the defined parent studies and continue to benefit from IP administration as evidenced by virologic control at the time of completion of the parent studies.

The duration of subject participation in the study will extend until age-appropriate formulations of DTG or ABC/DTG/3TC are available locally for each participant.

Overview of Study Design and Key Features	
Design Features	Continued access to DTG will be provided as follows: • Arm 1: Subjects from the IMPAACT P1093 parent study will continue to receive single entity DTG (Tivicay or Tivicay PD). • Arm 2: Subjects from the IMPAACT 2019 parent study will continue to receive ABC/DTG/3TC (Triumeq or ABC/DTG/3TC dispersible tablets).

Overview of Study Design and Key Features	
	Once subjects enter this rollover study, they will be seen in clinic every 12 weeks for safety visits until one of the events specified in protocol Section 4.2 occurs.
Study intervention	Subjects who complete DAIDS sponsored parent studies IMPAACT P1093 or IMPAACT 2019 continue to access DTG as follows: • Arm 1: Subjects from the IMPAACT P1093 parent study will continue to receive single entity DTG (Tivicay or Tivicay PD). • Arm 2: Subjects from the IMPAACT 2019 parent study will continue to receive ABC/DTG/3TC (Triumeq or ABC/DTG/3TC dispersible tablets).
Study intervention Assignment	Subjects who complete DAIDS sponsored parent studies IMPAACT P1093 or IMPAACT 2019 continue to access DTG and ABC/DTG/3TC respectively.
Interim Analysis	No interim analysis done
Final Analysis	No formal hypothesis testing will be performed. Data will provide only descriptive information on safety and tolerability.

2. STATISTICAL 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.

2.1. Multiplicity Adjustment

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.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Safety	• All participants who received at least one dose of study intervention once enrolled in the study.	• Safety

4. STATISTICAL ANALYSES

4.1. General Considerations

Guidance pertaining to the use of riociguat was incorporated. Riociguat dose may need to be reduced, consult the riociguat product labelling for dosing recommendations.

Guidance added to note that the pediatric weight-based once daily dose of DTG must be administered twice daily when ABC/DTG/3TC is co-administered 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.

Additionally, guidance added to note that the pediatric weight-based once daily dose of the single entity DTG must be administered twice daily when ABC/DTG/3TC is co-administered with the following other agents because they have known for potential enzyme induction activity;

- rifampicin
- carbamazepine
- phenytoin
- phenobarbital (barbiturates)
- St. John's wort

4.1.1. General Methodology

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category. The summaries decimal points (d.p) will be presented as follow:

- Mean, median, maximum, minimum will be +1 d.p the original values.
- std will be +2 d.p the original values.

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.1.2. Baseline Definition

For all endpoints (unless stated otherwise) the baseline value will be the latest pre-dose assessment for this study with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.3. Study Day

For analysis purpose, the analysis day will be calculated as (event day- first dose start day + 1 day) for events that occurred on or after first dose start date (e.g., visit, lab samples, AEs). In most cases day 1 visit will be the same as the final visit for the parent study (i.e. at or beyond Week 192 of the IMPAACT P1093 study or at or beyond Week 48 of the IMPAACT 2019 study).

4.2. Primary Endpoint Analyses

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). 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). This information should be copied from the protocol. Additional details may be added.

4.2.1 Definition of endpoint

- Adverse events:
    - Number and percentage of participants with SAEs
    - Number and percentage of participants with AEs Leading to discontinuation

4.2.2 Main analytical approach

All primary safety analyses (i.e. SAEs, AEs leading to treatment discontinuation and laboratory parameters analyses) will be based on the Safety population and presented by treatment group) i.e. DTG and ABC/DTG/3TC and enrolment weight band, unless otherwise specified.

4.2.3 Adverse Events Analyses

AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) using the latest version at time of database release. AEs will be graded by the investigator according to the Division of AIDS (DAIDS) Criteria Version 2.1.
As per protocol, all SAEs, and all AEs leading to treatment discontinuation, will be recorded from the time a subject provides consent to participate in the study and the study drug has been administered (at Day 1), up to and including any Follow-up Visit. Therefore, we will consider all recorded AEs in the data base as treatment emergent.
Summaries for SAEs and AE's leading to discontinuation will be produced using the data, and summaries by toxicity scale.

The following listings will be provided:

- All SAEs (including fatal SAEs)
- Drug Related SAEs
- AEs leading to discontinuation

All summaries will be presented by treatment arm and overall.

4.3. Other Endpoint(s) Analyses

HIV-1 RNA will be listed, if available, at each visit.

4.3.1. Secondary endpoint(s)

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).

4.3.2. Supportive secondary endpoint(s)

No supportive secondary endpoints.

4.4. Tertiary/Exploratory Endpoint(s) Analyses

No explanatory analyses.

4.5. Other Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Death

Summaries of death occurring for any reason and the reasons will be provided by visits and treatment. Death due to a disease related event will also be presented.

4.5.2. Extent of Exposure

- Number of days of on treatment will be calculated based on the formula:
  Duration of Treatment in Days = Treatment Stop Date – (Study Day 1) + 1
  This information will also be categorized as: < 12 weeks, 12 to 24 weeks, > 24 weeks to 48 weeks, > 48 weeks to 108 weeks, > 108 weeks

- Number of days of exposure to study drug will be calculated based on the formula:
  Duration of Exposure in Years = (Sum of Number of Days on Dose)/365
  This information will also be categorized as: < 12 weeks, 12 to 24 weeks, > 24 weeks to 48 weeks, > 48 weeks to 108 weeks, > 108 weeks

If there are any treatment breaks during the study, exposure data will be adjusted accordingly. Any subjects that changed dose during the study will be listed.

4.5.3. Adverse Events

As per protocol, all SAEs, and all AEs leading to treatment discontinuation, will be recorded from the time a subject provides consent to participate in the study and the study drug has been administered (at Day 1), up to and including any Follow-up Visit. Therefore, we will consider all recorded AEs in the data base as treatment emergent. All AE and SAE summaries will be by PT only unless otherwise specified.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs, and AEs leading to treatment discontinuation. The summary table will be displayed by preferred term (PT),by treatment arm, and overall .

4.5.3.1. Adverse Events of Special Interest

4.5.3.2. COVID-19 Assessment and COVID-19 AEs

This study was started in 2017 and continued during the COVID -19 pandemic. The information regarding the number of participants affected by COVID-19 and its symptoms will be reported according to GSK core standards. The visits impacted due to.the pandemic outbreak will be reported. Protocol deviations or adverse events related to COVID-19 if any, will also be reported according to GSK core standards.If the subjects have competed /withdrawn the study before the pandemic started in the respective countries according the COVID-19 dataset (with start date of pandemic in each of the countries), they will be considered as 'Not Related' to COVID-19.

4.5.4. Additional Safety Assessments (if applicable)

4.5.4.1. Vital Signs

Weights will be assessed and recorded on the eCRF for every visit except at the follow-up period. Their summaries (i.e. mean, median, SD, Q1, Q3, Max, Min) will be produced by visit and treatment.

4.5.4.2. Pregnancy Test

Summaries of pregnancy results will be listed if available, by treatment.

4.6. Other Analyses

4.6.1. Subgroup analyses

No subgroup analysis.

4.6.2. Other variables and/or parameters

No other variables or parameters.

4.7. Interim Analyses

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

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 06-JUN-2022).

5. SAMPLE SIZE DETERMINATION

Based on the design of the parent studies, it was anticipated that up to 300 participants could enrol into this study. Because of the nature of this study, no formal sample size determinations were made.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the efficacy analyses will be based on the Full Analysis Set and safety analysis and demographic and baseline tables and listings will be based on safety set. A summary of the number of participants in each analysis set will be provided.

In this multicentre global study, enrolment will be presented by country and site.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorized as ongoing.

Summary of subjects who enrolled or experienced screen failure will be populated. The percentages of overall screen failure, and by the screen failure reasons will be provided.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, sex, ethnicity, height/weight at screening and race will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 2 to <6 years, 6 to <12 years, 12 to <18 years, >18 years based on the safety set. Weight categories are summarized in Section 6.2.4.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

6.1.4. Prior and Concomitant Medications

Use of any disallowed medications at time of screening (see protocol Section 6.11.3 for a complete list of disallowed medications) will not be allowed to enroll to the study.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention.

On-Intervention is defined as time from first dose to last date plus 28 days. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: Lab and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window, i.e. > last dose date + xx days.

6.2.2. Study Day and Reference Dates

The reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.3. Assessment Window

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a target visit based on visit window. If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the earliest one will be taken in the slotting.

The visit window is as described by the Visit window Table 1.

Table 1 Visit window table

Visit	Protocol Target Day	Protocol Allowable Minimum	Protocol Allowable Maximum	Target ADY	ADY Minimum	ADY Maximum
Week 0	0			1	-42	42
Week 12	84	56	112	85	43	126
Week 24	168	140	196	169	127	180
Week 36	252	224	280	253	181	297
Week 48	336	308	364	337	298	378
Week 60	420	392	448	421	379	462
Week 72	504	476	532	505	463	546
Week 84	588	560	616	589	547	630
Week 96	672	644	700	673	631	714
Week 108	756	728	784	757	715	798
Week 120	840	812	868	841	799	882
Week 132	924	896	952	925	883	966
Week 144	1008	980	1036	1009	967	1050
Week 156	1092	1064	1120	1093	1051	1134
Week 168	1176	1148	1204	1177	1135	1219
Week 180	1260	1232	1344	1261	1220	1303
Week 192	1344	1316	1372	1345	1304	1387
Week 204	1428	1400	1456	1429	1388	1471
Week 216	1512	1484	1540	1513	1472	1555
Week 228	1596	1568	1624	1597	1556	1639
Week 240	1680	1652	1708	1681	1640	1722

This event indicates that every visit (after 12 weeks) there is a visit window of ± 4 up to the follow-up visit.

6.2.4. Weight Bands

The following weight bands in kilo grams (KG) will be used in the summary tables for each of the treatment

Weight Band (ABC/DTG/3TC)	Weight Band (DTG)
10 to less than 14 kg	10 to less than 14 kg
14 to less than 20 kg	14 to less than 20 kg
20 to less than 25 kg	Greater than 20
25 kg or greater	

6.2.5. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>

However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

▪ Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation

7. REFERENCES

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