IMPAACT P1093

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Pharmaceutical Support Provided by: GlaxoSmithKline

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Statistical Analysis Plan
(For Protocol Version 5, Letter of Amendment #1)

Version 4.0

April 22, 2021

This is IMPAACT P1093 SAP Version 4.0 with the names of authors and names of publication writing team members redacted

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1. Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcomes measures of P1093 that will be included in the primary manuscript, and which address the primary and secondary objectives of the study, focusing on analyses that address objectives for key safety, tolerability and efficacy outcome measures. The Primary SAP outlines the general statistical approaches that will be used in the analysis. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary statistical analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Statistical Analysis Report are included in the Analysis Implementation Plan (AIP). It is recognized that this statistical analysis plan (SAP) may be modified by the Study Team as new information becomes available or to reflect recommendations made by the SMC, if there are any.

It is noted here that all PK analyses will be done by the study pharmacologist who will draft a separate PK analysis plan.

Data for the Primary Statistical Analysis Report will be downloaded once the last participant of the last cohort has completed the Week 48 study visit, all queries have been resolved, and the database frozen for analysis.

The Primary Statistical Analysis Report will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is based on 48 weeks of treatment. A second submission to ClinicalTrials.gov will be done within one year after the last participant reaches Week 192 (the last week for long-term follow-up), at which time point the adverse event tables will be updated.

The tables, figures and listings of this Primary Statistical Analysis Report will be shared with the industry sponsors.

The SAP also includes analysis components that mainly support regulatory submission works as well as secondary manuscripts

Key Updates

Additional analyses will be done to present results by enrollment weight band
Name conventions for the Analysis populations were updated.

Added secondary virologic failure (VF) population and the corresponding data

summaries for the population.

Additional ad-hoc analyses (listing) assessing the impact of COVID-19 will be performed and the details will be included in the AIP.

Regulatory submission request: added the secondary analysis component of table summaries of emergent toxicities as well as figures summarizing laboratory test results and changes of these results over time (GSK/ViiV responsibilities)

2. Protocol Overview

2.1 Study Design

P1093 is a Phase I/II multi-center, open-label, non-comparative study of pharmacokinetic (PK) parameters, safety, tolerability, and efficacy of DTG in pediatric populations. Formulations will be evaluated with up to 300 HIV-infected infants, children and adolescents aged ≥ 4 weeks to < 18 years of age to be enrolled in the age-specific cohorts specified below:

Cohort I:	Adolescents ≥ 12 to <18 years of age (film-coated tablets)
Cohort IIA:	Children ≥ 6 to <12 years of age (film-coated tablets)
Cohort IIB:	Children ≥ 6 to <12 years of age (granules for suspension or dispersible tablets)
Cohorts III:	Children ≥ 2 to < 6 years of age (granules for suspension)
Cohort III-DT:	Children ≥ 2 to < 6 years of age (dispersible tablets)
Cohort IV:	Children ≥ 6 months to < 2 years (granules for suspension)
Cohort IV-DT:	Children ≥ 6 months to < 2 years of age (dispersible tablets)
Cohort V-DT:	Infants ≥ 4 weeks to < 6 months (dispersible tablets)

Participants receiving the film-coated tablet formulation were initially enrolled sequentially into Cohorts I and IIA. Granules for suspension were introduced in Protocol Version 3.0. When it subsequently became clear that dispersible tablets (DT) would be the commercially available pediatric formulation, new cohorts for DT were opened in Protocol Version 4.0. Under protocol Version 5.0, two formulations of DTG (film-coated tablets and dispersible tablets) will be evaluated; the target enrollment in Stage I was increased to allow for additional examination of PK, safety, and tolerability by enrollment weight bands, including participants from all of Cohorts III-DT, IV-DT, and V-DT. The approach for currently open cohorts III, IV and V is described below. However, additional cohorts and weight-band groups might be opened or reopened to investigate data gaps or new modifications to dosing, for example, regarding fasting requirements or background regimens.

The fundamental procedure for evaluation of DTG doses has remained unchanged through all protocol versions. Each cohort is enrolled in two sequential stages: Stage I and II. (The only exception is Cohort IIB which only enrolled through Stage I). In Stage I, participants undergo intensive PK sampling and are monitored for the safety and tolerability of DTG; to accept or reject a dose, the Protocol Team evaluates PK parameters exposures and 4-week safety and tolerability data. Once a treatment dose has been accepted, enrollment to Stage II begins to complete the cohort. Participants in Stage II will be followed for 48-weeks and evaluated for PK parameters (using population PK methods), safety and

tolerability. After study week 48 all Stage I and Stage II participants will transition to long-term follow-up and remain on study for approximately three additional years (144 additional weeks of follow- up, for a total of 192 on study). Study drug is provided for the duration of the study. Thereafter, participants are transitioned into care outside of the study.

Under Version 5, only Cohorts III-DT, IV-DT, and V-DT are open for accrual, and enrollment continues until a minimum of 10 participants in each cohort AND a minimum of 8 participants in each of the weight band groups below, are enrolled:

a) 3 to < 6 kg
b) 6 to < 10 kg
c) 10 to < 14 kg
d) 14 to < 20 kg

When the PK parameters and safety are determined acceptable among participants enrolled in Stage I, additional participants will be enrolled to Stage II (if necessary) to achieve a minimum of 22 participants per cohort receiving the acceptable dose for long-term safety evaluation.

Under previous versions of the protocol, enrollment begun for Cohort I and progressed to Cohort IIA once a preliminary dose of GSK1349572 for Cohort I had been determined based upon successfully meeting the PK and 4 week safety criteria in Stage I. Then, Cohort IIB started to enroll when Cohort IIA Stage I participants' PK and Week 4 safety data passed the criteria. Sequential enrollment for Cohorts III and IV proceeded in the same manner. Cohort V never enrolled because of the recommended changes in dosing and inclusion of enrollment weight band in the criteria for dose-finding.

For the dose-finding stage of this study, the data from Stage I of this study is analyzed in three steps, a mini-cohort analysis, an interim cohort analysis, and the full cohort/enrollment weight band group analysis (Section 3.1 of the protocol).

For the *mini-cohort analysis*, the overall safety and PK data of the first 4 participants with evaluable data in a given cohort will be evaluated with respect to the safety guidelines, per Section 8.5 and the PK guidelines, per Section 9.3 of the protocol.

The *interim cohort* analysis occurs when there are 10 participants with evaluable data in an age cohort. Data will be evaluated, and safety guidelines, per Section 8.5 and the PK guidelines, per Section 9.3 of the protocol.

For the *full Stage I cohort and enrollment weight band group* analysis, the starting dose of fully accrued cohorts are evaluated by both cohort and enrollment weight band group on the basis of 4-week safety (as per Section 8.5) and intensive PK data (as per Section 9.3). As of Version 5.0, the full analysis of Stage I data for Cohorts III-DT, IV-DT and V-DT occurs when all cohorts and enrollment weight band groups have met minimum enrollment targets and achieved 4-weeks of follow up (See Section 3.1 for more details).

Participants accrued to Stage II of the study will be administered the doses determined for their age cohorts, with no individual dose adjustments based on PK allowed. For purposes of analysis, data from these participants will be combined with the data from the Stage I participants who have been treated at the doses accepted for their cohorts and enrollment weight bands and who have not required

individual PK-determined dose adjustments, such that their total exposure to the study drug has been at the accepted dose. Sensitivity analyses will be performed to determine whether the exclusion of participants whose doses have been adjusted creates a selection bias which impacts upon any results.

Please note that the results of these dose-finding analyses will also be presented in the planned Primary Statistical Analysis Report mentioned above.

2.2 Hypothesis

DTG will be generally well tolerated and demonstrate an acceptable safety profile, adequate PK and antiviral activity when used concurrently with an optimized background therapy (OBT) in HIV-1 infected infants, children and adolescents.

2.3 Study Objectives and Outcome Measures

2.3.1 Primary Objectives and Outcome Measures

Primary Objectives

- To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily adult dose.

- To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.

- To evaluate the steady-state pharmacokinetics of DTG in combination with OBT in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C24h and AUC0-24 PK parameters in this population.

Primary Outcomes

- Toxicity through Weeks 24 and 48
    - All adverse events or lab toxicities of Grade 3 or higher severity
    - Adverse events or lab toxicities of Grade 3 or higher severity judged to be at least possibly attributable to the study medication
    - Termination from treatment due to a drug-related adverse event
    - Death
- Primary Response Variables (to be handled by the pharmacologist's analyses)
    - Pharmacokinetics: C24h, AUC0-24

2.3.2 Secondary Objectives and Outcome Measures

Secondary Objectives

- To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic

response in infants, children and adolescents at 24 and 48 weeks.

- To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.

- To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure.

- To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population PK analysis.

- To determine the extended long term (>48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents.

- To explore the relationship between DTG exposure and the antiviral activity.

- To evaluate pharmacokinetic, safety and tolerability profile of DTG when dosed by weight bands.

Secondary Outcome Measures

- Toxicity beyond Week 48 - aggregated, by cohort, by enrollment weight band:
  - All adverse events or lab toxicities of grade 3 or higher severity.
  - Adverse events or lab toxicities of grade 3 or higher severity judged to be at least possibly attributable to the study medication.
  - Termination from treatment due to a drug-related adverse event.
  - Death

- Plasma HIV-1 RNA (copies/mL) <400 copies/mL and <50 copies/mL- aggregated, by cohort, by enrollment weight band

- Pharmacokinetics (to be handled by the pharmacologist's analyses)
  - $AUC_{0\text{-}24}$, C_{24h}, C_0, C_{min}, Cm_{ax}, CL/F, $V_{z/F}$ and $t_{1/2}$

- Secondary response variables - aggregated, by cohort, by weight band
  - CD4/8 counts and percent
  - Genotypic and phenotypic measures of resistance at baseline and at virologic failure
  - Disease progression as measured by change in CDC category

3. Definitions

3.1 Baseline

For all endpoints (unless otherwise stated) the baseline value will be the latest pre-dose assessment 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 are missing, no derivation will be performed and baseline will be set to missing.

3.2 Analysis Populations

The analysis populations are updated as follows (for name conventions as well as relevance):

Safety Evaluable Population (definition per protocol for scientific analysis/report)

Participants who have taken at least 1 dose of DTG and were deemed safety evaluable by the Protocol

Team. In the primary scientific analysis, the safety population will exclude Stage I participants whose doses have been adjusted for inadequate PK. Stage I participants who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis. However, there are participants who might have been removed from PK analyses for reasons other than inadequate PK and who will still be included in the safety population in all analyses.

Safety Population (for the week 48 regulatory submission)
Participants who have taken at least 1 dose of DTG and were deemed safety evaluable by the Protocol Team.

Intent-To-Treat Exposed (ITT-E) Population (to replace All Treated Population or Efficacy Population)
All participants who were enrolled and have taken at least 1 dose of DTG.

Proposed Dose (PD) ITT-E Population: Participants whose exposure to DTG (ITT-E) has been based on the dose identified for the 2019 submission dossier, plus all additional participants enrolled into P1093 through Feb 2020.

Proposed Dose Safety Population (= Proposed Dose ITT-E Population)

Virological Failure (VF) Population (per protocol v5.0, section 6.5)

- A confirmed decrease in HIV RNA of < 1.0 log10 at or after week 12 unless the HIV RNA is < 400 copies/mL;
- A confirmed HIV RNA > 400 copies/mL starting at Week 24 or beyond on 2 consecutive measurements at least 1 week and within 4 weeks apart

Virologic REBOUND is also considered as virological failure and is defined as:

• Confirmed HIV-1 RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after an initial confirmed response (on 2 consecutive measurements at least 1 week apart) of HIV-1 RNA < 400 copies/mL;

• Confirmed > 1.0 log10 increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart). For the purposes of this study, nadir is defined as the lowest HIV-1 RNA while on study drug that is > 400 copies/mL.

4. Statistical Methods

4.1 General Considerations

For the week 48 analyses, the primary analyses will be based on the main analysis populations defined in Section 3.2. In particular, the safety, ITT-E and Proposed Dose (ITT-E or safety) populations. Sensitive and secondary analyses will be performed based on the subsets of main analysis populations and virological failure populations.

4.2 Visits and Evaluation Schedule

Entry of participants occurs within 30 days of screening. Intensive PKs occur at Day 5-10 or Week 2

(+/- 3 days). Thereafter, participants will have scheduled visits at Weeks 4, 8, 12, 16, 24, 32, 40 and 48. Participants who successfully complete 48 weeks of DTG treatment will continue on the study in long-term follow-up and will be seen in clinic every 12 weeks for approximately 3 additional years (192 weeks total). Further follow-up data to 240 weeks or beyond may be collected for those stay on study past 3 additional years

First dose date is considered as Day 1. STUDY DAY of assessment will be calculated as (Visit Date of Interest – First Dose Date +1). The nominal TARGET STUDY DAY of WINDOW for week is (7*week) + 1.

The week windows for all analyses, other than the analyses involving CD4/CD8 counts and percentages, will be as follows:

Study Day of Assessment	Assessment Window	Target Study Day of Window
-30 to 1	Week 0	1
2 to 21	Week 2	15
22 to 42	Week 4	29
43 to 70	Week 8	57
71 to 98	Week 12	85
99 to 126	Week 16	113
127 to 210	Week 24	169
211 to 252	Week 32	225
253 to 294	Week 40	281
295 to 378	Week 48	337
379 to 462	Week 60	421
463 to 546	Week 72	505
547 to 630	Week 84	589
631 to 714	Week 96	673
715 to 798	Week 108	757
799 to 882	Week 120	841
883 to 966	Week 132	925

Study Day of Assessment	Assessment Window	Target Study Day of Window
967 to 1050	Week 144	1009
1051 to 1134	Week 156	1093
1135 to 1218	Week 168	1177
1219 to 1302	Week 180	1261
1303 to 1386	Week 192	1345
1387 to 1470	Week 204	1428
1471 to 1554	Week 216	1512
1555 to 1638	Week 228	1596
1639 to 1722	Week 240	1680
> (Study Day of last dose + 1)	Follow-up	Study Day of last dose + 28

For CD4/CD8 count and percent analyses, the following week windows will be used:

Study Day of Assessment	Assessment Window	Target Study Day of Window
-3 to 1	Week 0	1
2 to 126	Week 12	85
127 to 210	Week 24	169
211 to 252	Week 32	225
253 to 294	Week 40	281
295 to 378	Week 48	337
> (Study Day of last dose + 1)	Follow-up	Study Day of last dose + 28

For the purposes of analysis, visit windows will be formed around each study visit using the midpoints between adjacent weeks as cutoffs. A window around a target Study Day will typically include all days from the midpoints between it and the target Study Days of the previous and the proceeding visits. If there are multiple evaluations within the analysis window for a given visit, the evaluation closest to the TARGET STUDY DAY of window, and the earlier measurement will be used if there are two measurements which are equally distant from the said target.

4.3 Analyses of outcome measures

4.3.1 Primary safety outcome

Purpose: to address whether DTG is safe among HIV-infected infants, children and adolescents aged ≥ 4 weeks to < 18 years of age.

Primary Safety Outcome Measures (presented in aggregate and by age cohort and enrollment weight band)

- All toxicity through Weeks 24 and 48
  - All adverse events or lab toxicities of Grade 3 or higher severity
  - Adverse events or lab toxicities of Grade 3 or higher severity judged to be at least possibly attributable to the study medication
  - Termination from treatment due to a drug-related adverse event
  - Death

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, will be used to grade all adverse events except for psychiatric events listed in Table 13 under Section 7.3 of the protocol, Version 5. The DAIDS AE Grading Table is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting.

Safety Analyses

Safety analysis for the regulatory submission will include all participants from the safety population as defined in Section 3.2.

In addition, the safety analysis for the scientific report will include participants from the safety evaluable population. Sensitivity analyses will be performed to determine whether the exclusion of participants whose doses have been adjusted creates a selection bias which impacts upon any results.

A subgroup analysis will be performed on participants in the Proposed Dose safety Population

Each participant's safety data will be summarized as: the worst grade of adverse event experienced during the first 24 weeks or 48 weeks of exposure to the study drug and the worst grade of adverse event judged to be at least possibly due to study drug during this time period.

Frequency distributions of the safety outcomes mentioned above will be presented in the aggregate and broken down by age cohort and by enrollment weight band.

Listings of all Grade 3+ events, will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of participants experiencing Grade 3+ adverse events will be presented in aggregate and broken down by age cohort and enrollment weight band, with these proportions bounded by exact 95% confidence intervals.

Similar analyses will present the proportions of participants exhibiting Grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

4.3.2 Secondary Outcome Measures

Secondary Outcome Measures (presented in aggregate, by cohort, and by enrollment weight band)

- All toxicity beyond Week 48
  - All adverse events or lab toxicities of grade 3 or higher severity.
  - Adverse events or lab toxicities of grade 3 or higher severity judged to be at least possibly attributable to the study medication.
  - Termination from treatment due to a drug-related adverse event.
  - Death
- Plasma HIV-1 RNA (copies/mL) <400 copies/mL and <50 copies/mL
- CD4/8 counts and percent
- Genotypic and phenotypic measures of resistance at baseline and at virologic failure
- Disease progression as measured by change in CDC category

Safety Analyses

Safety assessments will be performed on data collected beyond Week 48. The safety analyses for data beyond Week 48 will be similar to the primary analyses described above (section 4.3.1) and will include the Safety POPULATION participants. Another presentation of safety analysis results will include all participants in the PROPOSED DOSE SAFETY POPULATION.

Viral suppression Analyses

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at weeks 24 and48. Virologic outcomes at additional time points might also be evaluated. These analyses will be presented by age cohort and by enrollment weight band for the ITT-E POPULATION and PROPOSED DOSE ITT-E POPULATON.

For regulatory submission purposes, at both of week 24 or 48 time points the primary definition of virologic outcome will be calculated according to FDA's snapshot algorithm. Participants will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest. In addition, participants will be classified as virologic failures at either of these time points if they meet any of the following conditions prior to that time point:

a) Discontinuation of drug;
b) Change in background therapy not allowed in the protocol;
c) Change in background ART substitutions permitted per protocol, unless the decision to switch is documented as being before or at the first on-treatment visit after switching to OBT where HIV-1 RNA is assessed (Week 4) or participant's HIV-RNA is <400 copies/ml (or <50 copies/mL) before the switch.

The Snapshot algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of study drug prior to the visit window) as non-responders, as well as participants who switch their concomitant ART prior to the visit of interest in certain scenarios. ART substitutions permitted by the protocol (e.g., for toxicity reasons) are not penalized if the change happens while the subject is suppressed.

Otherwise, virologic success or virologic failure will be determined by the last available HIV-1 RNA

assessment while the subject is on-treatment within the visit of interest analysis window.

Virologic success includes participants who have HIV-1 RNA <400 copies/mL (or <50 copies/mL) at the visit of interest.

Virologic failure includes participants who changed any ART; participants who discontinued study drug or study before Week 48 for lack or loss of efficacy, discontinued while not < 50 c/mL/< 400 c/mL, and participants who have HIV-1 RNA ≥ 400 copies/mL (or ≥ 50 copies/mL)at the visit of interest.

Full details of the Snapshot algorithm are in Appendix.

The proportions of participants meeting the criteria for virological success at each of time points of analysis will be bounded by exact 95% confidence intervals, and will be presented in the aggregate and broken down by age cohort and by weight band.

HIV Drug Resistance Analyses
The incidence of HIV drug resistance will be presented descriptively at baseline and at the point of failure for participants who meet the criteria for virological failure per snapshot algorithm, Participants will be evaluated for HIV genotypic and phenotypic drug resistance to the OBT and to DTG.

Exploratory Analysis of Virological Failure (VF) Population: summaries of virologic failure participant characteristics, adverse events as well as drug resistance profiles will be presented

- Listing of selected baseline characteristics with ARV history
- Listing of grade 3+ laboratory adverse events
- Listing of SAE meeting ICH seriousness criteria
- Listing of serious laboratory adverse events meeting ICH seriousness criteria
- Listing of available phenotypic data (for participants with test results)
- Listing of resistance data for the virological failure participants

CD4/8 Analyses
Change in CD4/8 count and percent from baseline to weeks 24 and 48 will be bounded by 95% confidence intervals and presented in the aggregate and broken down by age cohort, by accrual to Stage I vs. Stage II, and by enrollment weight band for the ITT-E POPULATION and PROPOSED DOSE ITT-E POPULATION. Analysis results will be presented in aggregate, by age cohort and by enrollment weight band for the ITT-E POPULATION and PROPOSED DOSE ITT-E POPULATION.

Disease Progression as Measured by Change in CDC Category Analyses
Listing of participants who had changes in CDC category (to a worse category) while on study will be presented in aggregate, by age cohort, and by enrollment weight band for the ITT-E POPULATION and PROPOSED DOSE ITT-E POPULATION.
The stages will include the following: CDC Category Stage 1 at enrolment to Stage 3 event; CDC Category Stage 2 at enrolment to Stage 3 event; CDC Category Stage 3 at enrolment to New Stage 3 Event; CDC Category Stage 1, 2 or 3 at enrolment to Death.

Analysis of intensive pharmacokinetics of dolutegravir in cohorts III-V of participants who received the proposed dose of dispersible tablet (DT) (collaboration between study statisticians and pharmacologist)
A subset analysis is performed to assess the pharmacokinetics of dolutegravir: PK parameters of C_{24} and $AUC_{0\text{-}24}$, which were estimated via Phoenix WinNonlin version 6.3 and based on the whole blood samples collected at time 0 (before the dose) and at 1, 2, 3, 4, 6, 8 and 24 hours after ingestion; as well as the additional pharmacokinetic variables and tolerability, and clinical efficacy. The week 24 and 48 safety summary include outcomes of the grade 3 or great adverse events, termination of treatment due to drug related adverse event, or death. Efficacy summaries include virologic success defined as achieving a plasma HIV-1 RNA <400 copies/m; or the proportion achieving HIV-1 RNA <50 copies/mL and the change from baseline in CD4 cell count and percentage.

5. Core Manuscript Writing Team

Protocol Co-Chairs:

NIAID MO:
NICHD MO:
Study Statisticians:

Clinical Trial Specialists:

Data Managers:

Protocol Virologist:
Protocol Pharmacologist:

6. Protocol History

Protocol Version 1
Version 1.0 was implemented on December 14, 2010. One Clarification Memo (CM) and one Letter of Amendment (LOA) to Version 1 were issued: CM#1 (dated 3/1/2011) and LOA#1 (dated 3/1/2011).

CM#1, March 1, 2011
This CM provides clarifications to Section 5.0 – Study Treatment and to Appendix II – Planned Laboratory Testing on Collected Specimens in the P1093 Version 1.0 protocol.

LOA#1, March 1, 2011
This LOA is to provide to the "Parent Fact Sheet and Template Consent Form" for the NICHD sites participating in IMPAACT P1093 related to specimens collected for storage purposes.

Protocol Version 2

Version 2.0 was implemented on September 26, 2011.

Protocol Version 3

Version 3 was implemented on January 16, 2013. Three Clarification Memoranda (CM) and two Letters of Amendment (LOA) to Version 3 were issued: CM#1 (dated 5/6/2013), CM#2 (dated 12/3/2014) and CM#3 (dated 9/8/2015); LOA#1 (dated 3/8/2013) and LOA#2 9dated(11/15/2013)

CM#1, May 6, 2013

This CM provides clarification to specimens being shipped for genotyping at virologic failure, Appendix IA, IB, IC and ID for international laboratories.

CM#2, December 3, 2014

This CM addresses the following issues:

- As intended and consistent with the primary and secondary endpoints, the protocol has been clarified to indicate that AUC24 (primary PK endpoint) will be the primary pharmacokinetic variable and C24h (secondary PK endpoint) will be secondary in evaluating DTG steady-state pharmacokinetics and any subsequent dosing changes.
- An internal consistency in the protocol between Section 6.3, Appendix IE and the Sample Informed Consent Documents (amended via Letter of Amendment #1) regarding the frequency of visits during long term for subjects has been corrected to indicate that subjects receiving tablets will be seen every 12 weeks and those receiving granules will be seen every 8 weeks.
- The title of Appendix IG, the Schedule of Evaluations for Subjects who discontinue DTG has been corrected.

CM#3, September 8, 2015

This CM addresses two issues in protocol Version 3.0 as described below:

- Protocol Section 3.0 indicates that for participants enrolled in Stage I and not receiving antiretrovirals (ARVs) at entry, dolutegravir (DTG) should be started as monotherapy, and the ARV regimen would then be optimized immediately after completion of the 24 hour PK sampling. For operational clarity and internal consistency throughout the protocol this information has been reiterated in Section 6.23 and the Schedule of Evaluations.
- Dosing Tables D, E, and F have been updated to include a < 8 kg weight band dose

LOA#1, March 8, 2013

This LOA is to replace text that was inadvertently deleted under Section 4.0 (Inclusion Criteria), to update the laboratory performing the microalbumin/creatinine assay in South America, and to clarify the frequency of visits in the long term safety follow up per formulation in the sample informed consent.

LOA#2, November 15, 2013

This LOA is to change the dosing of GSK1349572 (dolutegravir, DTG) when used in combination with efavirenz (EFV), nevirapine (NVP), fosamprenavir (FPV)/ritonavir (r) or tipranavir/ritonavir (TPV)/r from once a day to twice a day.

Protocol Version 4

Version 4 was implemented on April 13, 2016. Four Clarification Memoranda (CM) to Version 4.0 were issued: CM #1 (dated 8 December 2016); CM#2 (dated 7 April 2017); CM#3 (dated 11 July 2017); and CM#4 (dated 30 January 2018). Protocol Version 5 was implemented on 7/12/2018.

CM #1, December 8, 2016:
This CM addresses inconsistencies in the protocol regarding the study drug regimen in Cohort II; the maximum in-use period of the granule formulation after reconstitution; and selection of the optimized background therapy (OBT) for participants entering Stage II. In addition, clarification regarding the intended interpretation of inclusion criterion 4.1.3.1, and the requirement for collection of samples for genotyping during long-term follow-up are added.

CM #2, April 7, 2017:
This CM clarifies the administration of optimized background therapy (OBT) for participants in Stage I receiving a failing ARV regimen that will continue as OBT. In addition, the Schwartz formula for evaluating renal function for 1-year-old participants is corrected.

CM #3, July 10, 2017:
This CM clarifies the guidelines for general toxicity management.

CM #4, January 30, 2018:
This CM serves to document the discontinuation of use of the granule for suspension formulation of dolutegravir (DTG) and the transition of participants currently receiving the granule formulation to the dispersible tablet formulation in IMPAACT P1093.

Protocol Version 5

Version 5 was implemented on July 12, 2018. Four Clarification Memoranda (CM) and one Letter of Amendment (LOA) to Version 5 were issued: CM#1 (dated 26 September 2018), CM#2 (dated 16 January 2019), CM#3 (dated 31 March 2020), and CM#4 (dated 8 April 2021); LOA#1 (dated 10 June 2020).

Changes from Version 4 to Version 5 are summarized below:

- Expansion of and updates to the relevant protocol sections and informed consent forms to include current data from P1093 and other adult studies on the safety and PK of DTG.
- Inclusion of updates to the relevant protocol sections and informed consent forms summarizing the interim analysis of an observational study from Botswana (Tsepamo) of women receiving DTG at the time of contraception.
- Inclusion of updates and clarifications to the relevant protocol sections and Schedules of Evaluations to ensure adequate and documented contraception use for female participants of child bearing potential.
- Inclusion of updates to the relevant protocol sections on the modeling and simulation of pharmacokinetic (PK) parameters to inform DTG dosing.
- Modification of the study design to include evaluation of dosing by weight band in addition to

age cohort, as weight-band based dosing is increasingly being recommended by WHO and other entities.

- Modification of the intensive PK sampling procedures to include analysis of intensive PK in a non-fasting state – if determined necessary – in addition to a fasting state as previously specified.
- Promotion of C24h to the primary PK parameter endpoint.
- Revision of the C24h and AUC0-24 targets for evaluation of PK as follows: For C24h, geometric mean (GM) target value of 995 ng/mL (changed from 750 ng/mL) with a range of 697 to 2260 ng/mL (changed from 500 – 2600 ng/mL). For AUC0-24, the GM target of 46 ug.h/mL remains unchanged and the range is modified to 37 to 134 ug.h/mL (changed from 37 – 86 ug.h/mL).
- Increase in the overall sample size to “up to 300” participants (from “up to 160”) to ensure adequate numbers of participants for assessment of weight-band based dosing in addition to assessment within age cohorts.
- Broaden eligibility criteria to include treatment-naïve participants of any age (rather than only treatment-naïve participants under two years of age). The inclusion of treatment-naïve children at any age is based on cumulative safety data, and the rationale that it is likely to be used and recommended as first-line therapy in children.
- Inclusion of updated toxicity management guidelines and supplemental parameters for psychiatric events consistent with the current Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
- Inclusion of updates to the protocol to reflect closure of Cohorts III and IV to further enrollment and removal of Cohort V which never opened to accrual; these three cohorts included the pediatric granule for suspension formulation which will not move forward for licensure. Evaluation of the film-coated tablets and dispersible tablets will continue under protocol Version 5.0.
- Inclusion of updates in the protocol and sample informed consent forms regarding entities who may access participant records.
- Modification of the sample informed consent forms to reflect all other protocol modifications, as needed.
- Incorporation of modifications included in prior clarification memoranda and letters of amendment associated with protocol Version 4.0.
- Other administrative corrections, clarifications and updates.
- Inclusion of a Protocol Signature Page.

CM#1, 26 September 2018:
This CM corrects an inconsistency in the dispensing procedures for dolutegravir dispersible tablets and clarifies the guidelines for establishing a laboratory normal value for indirect bilirubin.

CM#2, 16 January 2019:
This CM corrects inconsistencies related to the timing of primary safety and tolerability analyses; clarifies screening and enrollment procedures for weight-band groups; clarifies the timeline for resuming once daily dosing of dolutegravir after discontinuation of rifampin-containing tuberculosis (TB) treatment; and updates the Protocol Team Roster.

CM#3, 31 March 2020:
This CM is being issued to safeguard the health and well-being of IMPAACT P1093 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic. The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed for participant safety monitoring and to prioritize ongoing access and adherence to the study drug regimen.

CM#4, 8 April 2021:
This CM updates protocol specifications to reflect current policies of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH). It also updates the protocol team roster including the statisticians who work on the study. These updates do not impact the study design or study-specific procedures.

LOA#1, 10 June 2020:
This LOA includes the protocol team roster updates, the corrections and clarifications of protocol text that were included in corrected CM #1 (dated 26 September 2018), CM #2 (dated 6 January 2019), and CM #3, which was issued on 31 March 2020 to provide operational guidance for conducting study visits and procedures during the COVID-19 pandemic.

7. Appendix

7.1 Snapshot Approach – Detailed Algorithm Steps

Please note that no changes, re-optimization or intensification in background ARV therapy after initial optimization, which is defined per protocol section 6.3.1, will be permitted prior to protocol-defined virologic failure, with the exception of:

- a single substitution of a component of OBT with another approved compound for the management of drug toxicity
- formula substitutions (substituting single agents for fixed dose combinations and IMPAACT P1093, vice versa of the same ARV) – these are not classified as a change and are permitted during the study
- any changes discussed with and approved by the Protocol Team. Unless the change is specifically
  permitted, participants who have one or more new agents added to the optimized background regimen will be considered virologic failures.

Condition ('Week 48' indicates Week 48 window)	**Response**	**Reasons**
1. If ***non-permitted*** change in background therapy ***prior to*** Week 48	HIV1-RNA ≥ 50	Change in ART
2. If ***permitted*** change in background therapy ***prior to*** Week 48 AND the latest on-treatment VL prior to/on the date of change is ≥ 50 c/m [a]	HIV1-RNA ≥ 50	Change in ART
3: If ***non-permitted*** change in background therapy ***during*** Week 48		
• Last on-treatment VL during Week 48 prior to/on the date of change ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window and HIV-1 RNA >= 50 copies/mL
• Last on-treatment VL during Week 48 prior to/on the date of change <50 c/mL	HIV1-RNA < 50	
• No VL during Week 48 prior to/on the date of change	HIV1-RNA ≥ 50	Change in ART
4: If ***permitted*** change in background therapy ***during*** Week 48 AND the last on-treatment VL prior to/on the date of change is ≥ 50 c/mL [a]		
4.1 this last on-treatment VL occurs prior to Week 48	HIV1-RNA ≥ 50	Change in ART
4. 2 this last on-treatment VL occurs during Week 48 but prior to/on the date of change	HIV1-RNA ≥ 50	Data in window and HIV-1 RNA >= 50 copies/mL
5: If none of the above conditions met		
5.1 VL available during Week 48		
• Last on-treatment VL during Week 48 ≥ 50 c/mL	HIV1-RNA ≥ 50	Data in window and HIV-1 RNA >= 50 copies/mL
• Last on-treatment VL during Week 48 <50 c/mL	HIV1-RNA < 50	
a. No VL during Week 48		
i. if subjects still on study (i.e. IP has not been permanently stopped up to Week 48)	No virologic data at Week 48 Window	On study but missing data in window
ii. If subjects withdraw before/during Week 48 due to		
1. Safety reasons (e.g. AE/death, liver chemistry stopping criteria, renal toxicity withdrawal criteria, QTc withdrawal criteria et al, as recorded in eCRF Conclusion form)	No virologic data at Week 48 Window	Disc due to AE/death
2. Non-safety related reasons (e.g. Lack of efficacy, protocol deviation, withdrew consent, loss to follow-up, study closed/terminated, investigator discretion et al, as recorded in eCRF Conclusion Form)		
• Last on-treatment VL <50 c/mL OR no on-treatment VL available during study	No virologic Data at Week 48 Window	Disc for other reasons
• Last on-treatment VL ≥ 50 c/mL AND withdrawal due to Lack of efficacy	HIV1-RNA ≥ 50	Disc. for lack of efficacy
• Last on-treatment VL ≥ 50 c/mL AND withdrawal due to all other non-safety related reasons	HIV1-RNA ≥ 50	Dis. for other reason and HIV-1 RNA >= 50 copies/mL

Note the same process will be mapped out for Week 24. Also, note the same process will be mapped out for <400 c/mL.

Examples from FDA guidance

Data in Window

Virologic outcome should be determined by the last available measurement while the patient is on treatment and continued on trial within the time window:

- HIV-RNA = 580 copies/mL at Day 336, HIV-RNA below 50 copies/mL on Day 350. This should be categorized as HIV-RNA below 50 copies/mL.

No Data in Window

Discontinued study due to Adverse Event or Death:

- Any patient who discontinues because of an AE or death before the window should be classified as *Discontinued due to AE or Death* (as appropriate), regardless of the HIV-RNA result, even if the HIV-RNA is below 50 copies/mL at the time of discontinuation.
- However, if a patient has an HIV-RNA value in the time window and also discontinues in the time window, the viral load data should be used to classify the patient's response. This is the Virology First hierarchy:
    a. HIV-RNA below 50 copies/mL at Day 336 and discontinues because of AE or even dies on Day 360 — this person is categorized as having HIV-RNA below 50 copies/mL.
    b. HIV-RNA is 552 copies/mL on Day 336 and the patient discontinues on Day 360, the patient is categorized as having HIV-RNA greater than or equal to 50 copies/mL.

Discontinued for Other Reasons:

- Only patients who have achieved virologic suppression can be counted as *Discontinued for Other Reasons.*
- If a patient discontinues the study before the window because of *lack of efficacy* then the patient should be included in the HIV-RNA greater than or equal to 50 row and not in the Discontinued for Other Reasons row.
- If a patient discontinues because of *subject withdrew consent* and his or her HIV-1 RNA result at the time of discontinuation was equal to or above 50 copies/mL, then he or she should be categorized as HIV-RNA greater than or equal to 50 and NOT as Discontinued for Other Reasons.
- If a patient discontinued because of *Lost to Follow-Up* and the last HIV-RNA result was 49 copies/mL, then the patient can be categorized as Discontinued for Other Reasons while below threshold.
- If patients changed background treatment — *not permitted by protocol*— they should be considered an efficacy failure and captured in the HIV-RNA greater than or equal to 50 copies/mL row.

On study but missing data in window:

- If there are no data during Days 294 to 377, but there is an HIV-RNA below 50 copies/mL on Day 380, this patient should be considered *On Study but Missing Data in Window.*
- If there are no data during Days 294 to 377, but there is an HIV-RNA equal to or above 50 copies/mL on Day 280, this patient also should be classified as *On Study but Missing Data in Window.*

Optimized Background Therapy Substitutions After Randomization

- OBT substitutions (in-class or cross-class) permitted per protocol for documented toxicity reasons can be permitted on or before the first trial visit without penalty.

If OBT substitutions for toxicity reasons occur after the first trial visit, then patients should be categorized as having HIV-RNA greater than or equal to 50 copies/mL if they have HIV-RNA above 50 copies/mL at the time of switch.

7.2 SAP Version History

Version	Changes Made	Effective Date
1	Original Version	06/1/2012
2	Reflected changes in Protocol Version 5	01/17/2019
3	Added Mona Farhad as another Protocol Statistician; changed week window of baseline visit; clarified weight bands to mean enrollment weight band; included definition of PROPOSED DOSE POPULATION; and included PROPOSED DOSE POPULATION in all analyses	09/13/2019
4	Updated protocol statisticians: Peihua (Jessica) Liu and Kathryn P Gray (04/2021) via Protocol CM #4 The analysis populations (name conventions) were updated and secondary analysis (VF) population for the week 48 analyses and regulatory submissions were added. Specifically, • Safety Population • Safety Evaluable Population (needed for scientific analysis/report) • Intent-To-Treat Exposed (ITT-E) Population • Proposed Dose ITTE Population • Proposed Dose Safety Population • Virological Failure Population Other clarifications were added throughout the docs. Additional analyses were also included: Analyses assessing the impact of COVID-19; Analysis summary of virologic failure population; Analysis of intensive pharmacokinetics of dolutegravir in the proposed dose of dispersible tablet (DT) cohorts III-V.	12/23/2020