This is the IMPAACT 2019 SAP Version 1.0 with names of authors, names of publication writing team members and analysis timeline redacted.

IMPAACT 2019

Primary Statistical Analysis Plan

Version 1.0

Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Protocol Version 2.0

ClinicalTrials.gov Identifier: NCT03760458

December 05, 2019

Table of Contents

Version History

Version	Changes Made	Date Finalized
1	Original Version	12/5/2019

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of the IMPAACT 2019 study that will be included in the primary manuscript. The Primary SAP outlines the general statistical approaches that will be used in the analyses. 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 analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

It is noted here that all PK analyses including individual and summary tables will be done by the study pharmacologists and will be included in a separate PK analysis plan.

Analyses for the Primary Analysis Report will be finalized once the last participant has completed the Week 24 study visit, all queries have been resolved, and the study database closure/data lock through Week 24 has been completed. The Primary Analysis Report will include the primary and secondary outcome measures through Week 24. This report will form the basis for initial result reporting to ClinicalTrials.gov. Initial result reporting needs to happen 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 the date of the last Week 24 visit.

Secondary outcomes through Week 48 will be addressed in a secondary analysis report which will form the basis for additional results reporting to ClinicalTrials.gov. The second submission to ClinicalTrials.gov will be done within one year after the last Week 48 visit, at which time point the relevant analyses through Week 24 will be updated.

A final submission to ClinicalTrials.gov will be done within one year after the last Week 144 visit, at which time point the relevant analyses will be updated.

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

As this study will have regulatory submission, all analyses covered in this primary SAP will be included as part of the regulatory submission. The exploratory outcome measures will be described separately.

2 Study Overview

2.1 Study Design

IMPAACT 2019 is a Phase I/II, multi-site, open-label, multiple dose, non-comparative study to assess the pharmacokinetics (PK), safety, and tolerability of fixed dose combination abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) in HIV-infected children less than 12 years of age.

Up to 75 participants will be enrolled to achieve at least five dose evaluable participants in each weight band and at least 50 participants overall (at least 25 less than six years of age and at least 25 six to less than 12 years of age).

Dispersible tablets containing 60 mg ABC, 5 mg DTG, and 30 mg 3TC and immediate release tablets containing 600 mg ABC, 50 mg DTG, and 300 mg 3TC, administered for at least 48 weeks and up to 144 weeks in weight bands as follows:

	Weight Band	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)

Accrual is expected to require approximately 12 months; enrolled participants will be followed for at least 48 and up to 144 weeks, so the whole study will take approximately 48 months in total.

2.2 Hypotheses

1. Selected doses of ABC/DTG/3TC dispersible and immediate release tablets will achieve protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age.

2. ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets will be described as safe for treatment in children less than 12 years of age.

2.3 Study Objectives

2.3.1 Primary Objectives and Outcome Measures

1. Determine the steady-state $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} of ABC, DTG, and 3TC and confirm the dosing of ABC/DTG/3TC dispersible and immediate release tablets that achieves protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age

   Outcome measures (will be included in the PK report generated by the study pharmacologist):
   - Geometric mean $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} for ABC, DTG, and 3TC based on analysis of intensive PK samples collected at Week 1 ($AUC_{0\text{-}24h}$ and C_{24h} to be compared within each weight band to the PK targets specified in Section 10.3.1 of protocol)

2. Evaluate the safety profile of 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

   Outcome measures:
   - All adverse events occurring through Week 24
   - Participants with the following adverse events through Week 24:
     - Grade 3 or Grade 4 adverse events assessed as related to study drug
     - Grade 5 adverse events assessed as related to study drug
     - Life-threatening adverse events assessed as related to study drug
     - Serious adverse events assessed as related to study drug
     - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug

2.3.2 Secondary Objectives and Outcome Measures

1. Determine the PK of ABC, DTG, and 3TC, and clinical covariates that influence PK disposition, among children less than 12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with ABC/DTG/3TC dispersible and immediate release tablets

   Outcome measures (will be included in the PK report generated by the study pharmacologist):
   - $AUC_{0\text{-}24h}$, C_{0h}, C_{24h}, C_{max}, T_{max}, CL/F, and $t_{1/2}$ derived from population PK modeling with sampling through Week 48

2. Evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

   Outcome measures:
   - All adverse events occurring through Week 48
   - Participants with the following adverse events through Week 48:
     - Grade 3 or Grade 4 adverse events assessed as related to study drug
     - Grade 5 adverse events assessed as related to study drug
     - Life-threatening adverse events assessed as related to study drug
     - Serious adverse events assessed as related to study drug
     - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug

   - All adverse events occurring through Week 144
   - Participants with the following adverse events through Week 144:
     - Grade 3 or Grade 4 adverse events assessed as related to study drug
     - Grade 5 adverse events assessed as related to study drug
     - Life-threatening adverse events assessed as related to study drug
     - Serious adverse events assessed as related to study drug

- Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug

3. Evaluate virologic and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

   Outcome measures:
   Virologic responses:
   - HIV-1 RNA through Week 48
   - HIV-1 RNA through Week 144
   - Participants with:
     - HIV-1 RNA ≥200 copies/mL at Weeks 4, 24, and 48 (the FDA's snapshot algorithm)
     - HIV-1 RNA ≥50 copies/mL at Weeks 4, 24, and 48 (the FDA's snapshot algorithm)

   Immunologic responses:
   - CD4+ cell count and percentage at Weeks 4, 24, and 48
   - CD4+ cell count and percentage through Week 144

4. Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

   Outcome measures:
   - Total cholesterol, HDL, LDL, and triglycerides at Weeks 24 and 48

5. Evaluate adherence to and palatability and acceptability of ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age at 4, 24 and 48 weeks of treatment

   Outcome measures:
   - Parent/guardian reported adherence to study drug at Weeks 4, 24, and 48
   - Parent/guardian reported tolerability (i.e., palatability and acceptability) of study drug at Weeks 4, 12, 24, and 48

6. Evaluate HIV-1 genotypes and phenotypes among children less than 12 years of age who experience virologic failure while receiving treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets

   Outcome measures:
   - ARV resistance mutations at time of virologic failure (and at entry for children with resistance identified at time of virologic failure)

2.4 Overview of Formal Interim Monitoring

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly. Routine SMC reviews will occur at least annually and on a more frequent or ad hoc basis if any safety issues or concerns arise (Details about these reviews are outlined in protocol Section 9.5.2 and the SPDSMP). The first routine review will take place approximately six months after the first participant is enrolled in the study, unless otherwise specified by the SMC. The SMC will also review safety and intensive PK outcomes and the Clinical Management Committee (CMC)'s assessment of the appropriateness of each weight band dose. In addition to the above, the SMC may conduct ad hoc or triggered safety reviews, for which more limited data may be provided, focusing on the events that triggered the reviews. Triggered reviews will occur in the following scenarios:

(1) In the event of any adverse event that is fatal or life-threatening, the CMC will review the event as soon as possible (ideally within three business days of site awareness) and assess its relationship to study drug:
   - If either the site investigator or the CMC assesses the event as related to study drug, accrual into all weight bands will immediately be paused. An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
   - If the site investigator and the CMC assess the event as not related to study drug, participant accrual will continue. The SMC will be informed of the event along with the CMC's assessment and decision-making.

(2) If, after dose confirmation for a given weight band is completed, more than 25% of the children enrolled in that weight band experience grade 3 or higher adverse events assessed by the site investigator as related to study drug or adverse events assessed by the site investigator as related to study drug that result in permanent discontinuation of study drug, an ad hoc SMC review will be convened. The SMC will review all relevant safety and pharmacokinetic data, along with the recommendations of the CMC, and determine whether and under what conditions further accrual into the study may proceed.

The CMC may also request an SMC review of any other adverse event or trend of concern. The CMC may likewise request an SMC review in the event of an unresolvable disagreement within the CMC on an issue that would impact decision-making. The CMC may choose to pause participant accrual and/or administration of study drug pending the outcome of the requested SMC review.

2.5 Dose Confirmation for Each Weight Band

An initial group of 5-7 children will be enrolled in each weight band and undergo intensive PK sampling at Week 1. The CMC will review intensive PK and four-week safety data for these children at least monthly until dose confirmation has been completed for each weight band. Dose confirmation will be based on dose-evaluable children as defined in Section 3.2 of protocol Version 2.0. The CMC will take action as needed according to the PK guidelines and the safety guidelines.

- If data from the dose-evaluable children in the weight band meet the PK and safety guidelines, and there are no safety concerns based on all available data from all weight

bands, the dose will be considered appropriate for the weight band and the SMC will be notified.

- If data from the dose-evaluable children in the weight band fail the PK or safety guidelines, or there are safety concerns from other weight bands, and the Protocol Team determines that an adjusted dose and/or alternative dosing strategy is needed to safely achieve targeted drug concentrations, accrual into the weight band will be paused and the SMC will be notified. Following consultation with the SMC, and unless other recommendations are provided by the SMC, 5-7 additional dose-evaluable children will be enrolled into the weight band and the adjusted dose will be evaluated as described above.

- If data from other children who are evaluable for safety or PK but not both (i.e., are not dose-evaluable), are available when dose confirmation analyses are performed, these data may be included in the analyses.

- If a confident determination regarding achievement of the PK targets cannot be made, additional children enrolled in the weight band will undergo intensive PK sampling. The PK analysis for the weight band will then be repeated with data from the initial 5-7 children and the additional children.

Unless the criteria specified below for pausing participant accrual are met, enrollment into each weight band and into the study overall will not be paused while PK and safety data are being reviewed.

Safety Guidelines for Dose Confirmation:

The frequency of adverse reactions occurring among the first 5-7 participants through Week 4 will be closely monitored. If any of these safety-evaluable participants experiences a fatal or life-threatening event that is assessed as related to study drug, or if more than 25% of the participants experience a related grade 3 or higher non-fatal and non-life-threatening adverse event or a related adverse event that results in permanent discontinuation of study drug, the dose under evaluation will be considered to have failed the safety guidelines. Otherwise, and absent any safety concerns from other weight bands, the dose will be considered to have passed the safety guidelines.

PK Guidelines for Dose Confirmation:

Dose confirmation within each weight band will be based on achieving a geometric mean DTG $AUC_{0\text{-}24h}$ between 35.1 and 134 µg·h/mL and C_{24h} between 0.67 and 2.97 µg/mL, and geometric mean ABC and 3TC $AUC_{0\text{-}24h}$ between 6.3 and 50.4 µg·h/mL and 6.3 and 26.5 µg·h/mL, respectively. Note: please see Section 10.3.1 of Protocol Version 2.0 for detailed information regarding PK guidelines for dose confirmation. In addition, the protocol pharmacologists will prepare the PK analysis plan to describe how the PK data will be described and summarized.

3 Statistical Principles

3.1 Definition of Baseline

For some outcome measures, baseline values will be determined and changes from baseline will be analyzed. For analyses purposes, baseline value is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 (First dose date is considered as 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 General Considerations

For participants who were inadvertently enrolled and later found to be ineligible, if they received the study treatment drug, their safety data will be summarized separately; if they never started the study treatment drug, together with other participants who never started treatment drug, they will only be included in the accrual tables and will be excluded from all analyses.

Participants with dose adjustments due to weight change, i.e., participants who have dose adjustments due to weight gain or decrease, will be analyzed in their original weight band in which they enrolled.

For participants whose study drug dose is adjusted for reasons other than weight gain or decrease (including participants whose study drug regimen is modified due to receipt of rifampin-containing TB treatment), safety data up to the date of dose adjustment will be analyzed in the original weight band, and sensitivity analyses will be performed to assess whether conclusions drawn from primary dose confirmation evaluations would be affected by inclusion of these data. Safety data for these participants after the date of dose adjustment will be described separately.

Primary and secondary analyses will be done for the “primary safety population”, which is defined as participants (1) whose starting dose of ABC/DTG/3TC is the final confirmed dose for their weight band and (2) whose dose may have been increased due to weight gain putting them in a higher weight band, provided that the dose received in the higher weight band is the dose that would be recommended in the overall patient population who experience a similar weight band progression. Participants whose treatment is consistent with (1) and (2) above, but who discontinue treatment due to toxicity before Week 24 will be included and treated as safety failures in the primary safety analyses. In addition, secondary analyses will also be done for participants who received at least one dose of study drug, which includes participants whose study drug doses were modified due to other reasons (not due to weight gain) or who received doses other than the final confirmed dose for their weight band. Results will be presented by weight band and in aggregate.

3.3 Analysis Approaches

3.3.1 Primary Safety Outcome

The primary safety analyses will be done for the “primary safety population” as defined in Section 3.2. These primary analyses will be performed after the last participant has completed his or her Week 24 Visit, all queries have been resolved, and the study database closure/data lock through

Week 24 has been completed. Results will be presented by weight band and in aggregate, as well as by age group and study drug formulation.

A listing of all adverse events of all severity grades will be summarized. When analyses involve assessment of relationship to study drug, the site investigator's assessment will be used.

In addition, overall proportions (bounded by exact 95% CIs) of participants experiencing any of the following events and proportions (bounded by exact 95% CIs) experiencing each type of event will be presented:

- Grade 3 or higher adverse events
- Grade 3 or Grade 4 adverse events assessed as related to study drug
- Grade 5 adverse events assessed as related to study drug
- Life-threatening adverse events assessed as related to study drug
- Serious adverse events assessed as related to study drug
- Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug

Each participant would only be counted once for each of the proportion, even if they experience more than one event of that category.

Listings of all grade 3 or higher adverse events, grade 3 or grade 4 adverse events assessed as related to study drug, grade 5 adverse events assessed as related to study drug, life-threatening adverse events assessed as related to study drug, serious adverse events assessed as related to study drug, and adverse events assessed as related to study drug that result in permanent discontinuation of study drug will be provided by System Organ Class and Preferred Terms.

The proportion of participants meeting each of the criteria above that trigger an SMC safety review will be presented descriptively.

For regulatory submission purposes, all the above analyses will be performed and will include all participants. Frequency distributions of safety outcomes will be presented by weight band and in aggregate, as well by age group and study drug formulation.

3.3.2 Secondary Outcome Measures

Secondary Safety Outcome

The primary safety analyses described in Section 3.3.1 will be repeated as secondary analyses for the "primary safety population" as defined in Section 3.2, but include safety outcomes from the on-treatment date through Week 48, and separately from the on-treatment date through Week 144.

In addition, further analyses that include safety outcomes from on-treatment date through Week 24, Week 48, and Week 144 for all participants who received at least one dose of study drug will be performed.

Descriptive and exposure-related analyses will present safety outcomes for participants whose study drug doses were modified due to weight band dose adjustment or who otherwise received doses other than the final confirmed dose for their weight band. This will include data representing the final dose for each weight band, as well as data representing doses considered to have failed.

For each starting dose, all grade 3 or higher adverse events will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event, and the site investigator's assessment of relationship to study drug.

Virologic Response

Analyses for virologic response will be done for participants "primary safety population" as defined in Section 3.2 and for all participants who received at least one dose of study drug, respectively. Results will be presented by weight band and in aggregate.

HIV-1 RNA data will be analyzed descriptively and using the FDA snapshot algorithm.

Descriptive analyses will include HIV-1 RNA available at all time points and will present the number and percentage of participants with a suppressed viral load (with cutoff of 200 copies/mL) at each time point and the distribution of non-suppressed viral load values at each time point. HIV-1 RNA at each time point for each participant will use the last available HIV-1 RNA assessment while the participant is on study drug within the allowable study visit window. Data will be presented separately for participants who were ART-naïve versus ART-experienced at study entry, as well as for participants with a documented M184V mutation, who will undergo additional HIV-1 RNA testing per the Schedule of Evaluations.

For analysis using the FDA snapshot algorithm, HIV-1 RNA values for participants will be assessed at Weeks 4, 24 and 48. At each time point, the FDA's snapshot algorithm will be used for the definition of virologic outcome, with cutoffs of 200 copies/mL or 50 copies/mL (analyses will be performed twice, once at the 200 copies/mL threshold and separately at the 50 copies/mL threshold). In addition, participants will be classified as virologic failures if they prematurely discontinued study drug prior to Week 4, Week 24, or Week 48. Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on study drug within the visit of interest window. The proportions of participants meeting the criteria for virologic failure or success at each time point will be bounded by exact 95% CIs and will be presented both in the aggregate and by weight band.

Immunologic Response

Analyses for immunologic response will be done for participants "primary safety population" as defined in Section 3.2 and for all participants who received at least one dose of study drug, respectively. Results will be presented by weight band and in aggregate.

Median and the associated interquartile range for changes in CD4+ count and percentage from baseline to Weeks 4, 24, 48 for participants will be presented by weight band and aggregated, bounded by 95% CIs. Missing CD4+ values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline CD4+ values.

Total Cholesterol, HDL, LDL, and Triglycerides

Analyses for total cholesterol, HDL, LDL, and triglycerides will be done for participants "primary safety population" as defined in Section 3.2 and for all participants who received at least one dose of study drug, respectively. Results will be presented by weight band and in aggregate.

Median and the associated interquartile range for changes in total cholesterol, HDL, LDL, and triglycerides from baseline to Weeks 24 and 48 for participants will be presented by weight band and aggregated. Missing total cholesterol, HDL, LDL, and triglyceride values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline values.

Adherence, Palatability and Acceptability

Adherence, palatability and acceptability measures — based on questionnaire responses — will be summarized by weight band and aggregated for all participants who received study drug.

As palatability and acceptability data are accumulated in the study, if the Protocol Team determines that the dispersion volumes shown in protocol Table 8 are not sufficiently acceptable for children in weight band #3 or #4, the volumes shown in protocol Table 9 may be recommended for all applicable participants. It is generally expected that these data will be reviewed after approximately 20-30 children in these weight bands have completed their Week 4 visits; however, this determination may be made at any time in response to accumulating study data. The Protocol Team will use responses to item 3 of the Palatability Assessment (QLW10081) and item 7 of the Acceptability Assessment (QLW10080) at Week 4 to make this determination. More specifically, the volumes specified in protocol Table 8 will be considered preferred if at least half of children (their caregivers) answer QLW10081 item 3 with a response of very good, good, or average and at least half of children (their caregivers) answer QLW10080 item 7 with a response of it is acceptable.

These data will be presented descriptively.

Antiretroviral Resistance

Participants with confirmed virologic failure will be evaluated for viral resistance to the components of the study drug regimen. For these participants, both phenotypic and genotypic resistance results will be presented descriptively.