Approvals

IMPAACT 2023

Primary Statistical Analysis Plan

Version 2.0

18 August 2025

A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1

ClinicalTrials.gov Identifier: NCT05406583

Protocol Version 2.0

This is IMPAACT 2023SAP Version 2.0 with names of authors, names of publication writing team members and analysis timeline redacted.
Due to the fact that genotype data was not available, the analysis of other objectives described in section 5 of the SAP was not pursued.

Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health

Table of Contents

Table of Tables

Version History

Version	Changes Made	Date Finalized
1.0	Original Version	01 April 2022
2.0	Sections 3 and 8: Changed timing of generation of the Primary Analysis Report to allow timely completion of the regulatory submission deliverables; Section 3.2: added tolerability analysis windows; Sections 4.1.3 and 4.1.4: clarified participants included in tolerability analysis; throughout: minor clarifications and updates.	18 August 2025

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and key secondary estimands and other outcome measures for IMPAACT 2023, focusing on analyses that address the study objectives for study drug safety and tolerability. It includes a full description of the estimands and general analytic approaches of the primary, secondary and other outcome measures. It describes the analyses for the study objectives that will be in the primary manuscript(s) or submitted to ClinicalTrials.gov (regardless of the reporting timeline).

The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, to ensure agreement on the statistical analyses to be performed and presented in the reports addressing the study objectives. Specifications in the Primary SAP will be used for the Final Analyses Reports and Regulatory Submissions Report(s). The Final Analyses Reports will form the basis for the primary study manuscripts and results reporting to ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions will be included in the Analysis Implementation Plan (AIP).

It is noted that analyses related to pharmacokinetic (PK) study objectives will be done by the Protocol Pharmacologists. Refer to the separate Pharmacology Analysis Plan developed by the Protocol Pharmacologists for an outline of analyses for PK-related objectives and outcome measures.

1.2 Version History

Version 1.0 of the Primary SAP matched the specifications in Protocol Version 2.0, since the study did not open to accrual under Protocol Version 1.0.

Major modifications in Primary SAP Version 2.0 include changing the timing of generation of the Primary Analysis Report to allow timely completion of the regulatory submission tables, figures, and listings package (Sections 3 and 8); adding tolerability analysis windows (Section 3.2); clarifying participants included in tolerability analysis (Sections 4.1.3 and 4.1.4).

2 Study Overview

2.1 Overview of Study Design

IMPAACT 2023 is a Phase I, multi-site, open-label, non-comparative dose-finding study to evaluate the safety, tolerability, and PK of Dolutegravir (DTG) when added to an infant's standard HIV-1 antiretroviral (ARV) prophylaxis. DTG is the study drug and two formulations may be used in the study as follows:

- DTG 5 mg/mL liquid suspension
- DTG 5 mg dispersible tablet (DT)

Singleton, generally healthy, full-term (≥ 37 weeks gestation at birth), with birth weight ≥2 kg infants of mothers living with HIV-1 will be screened and enrolled to the study. Infants with a positive HIV-1 test result at screening/entry, known maternal-fetal blood group incompatibility, prior exchange transfusion or elevated bilirubin that requires treatment with exchange transfusion, or receiving or will be receiving (as infant medication or through breastmilk) any of the disallowed medications in protocol Section 5.8.1 will be excluded from the study. The infant and mother will be enrolled as a pair when the infant is 0-5 days of life, with the mother taken off study after completing the Entry visit and the infant taken off study after completing the Week 16 visit (Days 112-140 of life). Infants, but not the mothers will receive the study drug DTG. Infants will be enrolled in one of two sequential dosing cohorts: Cohort 1 (two single DTG doses approximately seven days apart) and Cohort 2 (chronic DTG dosing through Week 4 or 6 visit while infant is on local standard of care for ARV prophylaxis regimen). Cohort 1 is intended to generate the PK and safety data that will inform the DTG starting dose and formulation for Cohort 2.

To account for possible impact of infant's *in utero* exposure to maternal DTG and how this may affect the infant's initial DTG dosing (i.e., timing and/or strength), at study entry in both cohorts, the mother-infant pair will be stratified based on the infant's *in utero* exposure to maternal DTG (DTG-naïve and DTG-exposed groups) using the criteria below:

- DTG-naïve: Infant born to a mother who did not receive DTG during the two weeks immediately prior to delivery.
- DTG-exposed: Infant born to a mother who received at least one dose of DTG less than or equal to 72 hours prior to delivery.

  Note: Mother-infant pairs in which the mother received at least one dose of DTG more than 72 hours and within two weeks prior to delivery will not be enrolled in the study.

Across the two cohorts there will be up to five study strata.

Table 2-1: Description of the Study Strata

Cohort	Infant *in utero* DTG exposure	Study Stratum	
		Designation	**Description**
Cohort 1	DTG-naïve	Stratum 1A	DTG-naïve infants receiving 2 doses of DTG liquid suspension, with 1st dose at 0-5 days of life and 2nd dose at the 7 Days Post Initial Dose visit
	DTG-exposed	Stratum 1B	DTG-exposed infants receiving 2 doses of DTG liquid suspension, with 1st dose at 2-5 days of life and 2nd dose at the 7 Days Post Initial Dose visit
	DTG-naïve	Stratum 1C*	DTG-naïve infants receiving 2 doses of DTG dispersible tablet, with 1st dose at 0-5 days of life and 2nd dose at the 7 Days Post Initial Dose visit

Cohort 2	DTG-naive	Stratum 2A	DTG-naïve infants receiving chronic dosing of DTG through Week 4 or 6 visit based on duration of local standard ARV prophylaxis (4-6 weeks)
	DTG-exposed	Stratum 2B	DTG-exposed infants receiving chronic dosing of DTG through Week 4 or 6 visit based on duration of local standard ARV prophylaxis (4-6 weeks)

* If PK and safety data from Strata 1A and 1B do not support the use of a DTG 5 mg dose then Stratum 1C will not enroll.

This study does not involve any randomization and mother-infant pairs will be enrolled into the cohort that is open to study accrual.

Cohort 1 (two single DTG doses approximately seven days apart): A minimum of 12 and up to 36 mother-infant pairs (across strata) will be enrolled to achieve six evaluable infants in each stratum receiving the DTG dose that informs the starting dose regimen for Cohort 2. Strata 1A and 1B will be enrolled concurrently, and infants will receive DTG 0.5 mg/kg liquid suspension. Stratum 1C will only enroll if the Strata 1A and 1B PK and safety data support administration of the DTG 5 mg DT in all eligible neonates or in neonates with a minimum weight.

Cohort 2 (chronic DTG dosing through Week 4 or 6 visit based on the duration of local standard ARV prophylaxis (4-6 weeks): A minimum of 24 (12 in each stratum) and up to 72 mother-infant pairs (across both strata) will be enrolled to achieve 12 evaluable infants in each stratum receiving the final proposed chronic DTG dose regimen. At least eight breastfeeding and eight formula-feeding infants will be enrolled in Cohort 2 across both strata.

The study duration will be approximately 28 months total. Accrual is expected to require approximately 24 months.

2.2 Hypothesis

DTG, when added to an infant's standard HIV-1 ARV prophylaxis, is well tolerated in neonates and young infants and can be safely administered to achieve adequate drug exposure for prevention of HIV-1.

2.3 Study Objectives and Outcome Measures

This Primary SAP addresses the following primary, secondary and other study objectives with their corresponding outcome measures. Study results for primary and secondary objectives will be submitted to ClinicalTrials.gov.

The following specifications will be used for the safety outcome measures:

- AE attribution to study drug will be based on site assessment, unless the Study Monitoring Committee (SMC) was consulted, in which case the SMC's opinion will be used.
- The Safety Analysis Windows defined in Section 3.3 will be used to define the timeframe for the safety outcome measures.

- "Day 0" is the day of the infant's birth.

2.3.1 Primary Objectives and Outcome Measures

2.3.1.1 To evaluate the safety and tolerability of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.

Safety outcome measures (primary):

1) **The proportion of infants classified as study drug-related safety failures.**
An infant is classified as a study drug-related safety failure for the primary safety study objective if any of the following occurred after the initial study drug dosing through two weeks after permanent discontinuation of the study drug (i.e., two weeks after off treatment date):
   - Death (i.e., Grade 5 AE) assessed as related to the study drug, or
   - Grade 3 or 4 AE assessed as related to study drug, or
   - Life-threatening AE assessed as related to study drug, or
   - AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug

2) **The proportion of infants classified as safety failures.**
An infant is classified as a safety failure for the primary safety study objective if any of the following occurred after the initial study drug dosing through two weeks after permanent discontinuation of the study drug (i.e., two weeks after off treatment date):
   - Grade 3 or 4 AE, or
   - Death (Grade 5 AE)

Tolerability outcome measure:

3) **The proportion of infants who are not able to tolerate the study drug.**
An infant is considered not able to tolerate the study drug if the infant experiences problems taking the study drug as defined in Protocol Section 6 or experiences any AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug. Tolerability will be assessed after the initial study drug dosing through study drug discontinuation (i.e., up to Week 6).
Note: The study has study-specific Study Drug Tolerability eCRFs to collect information on infant problems in taking the study drug.

2.3.1.2 To evaluate the pharmacokinetics of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.

Note: Please refer to the Pharmacology Analysis Plan for the outcome measure.

2.3.1.3 To propose an appropriate DTG dose regimen during the first four weeks of life for HIV-1-exposed infants.

Note: There is no separate outcome measure for this objective.

2.3.2 Secondary Objective and Outcome Measures

2.3.2.1 To evaluate the safety of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first 16 weeks of life.

Safety outcome measures (secondary):

1) **The proportion of infants classified as study drug-related safety failures.**
An infant is classified as a study drug-related safety failure for the secondary study safety objective if any of the following occurred after the initial study drug dosing through Week 16 (i.e., Day 140):
- Grade 3 or 4 AE assessed as related to study drug, or
- Death (Grade 5 AE) assessed as related to the study drug, or
- Life-threatening AE assessed as related to study drug, or
- AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug

2) **The proportion of infants classified as safety failures.**
An infant is classified as a safety failure for the secondary study safety objective if any of the following occurred after the initial study drug dosing through Week 16 (i.e., Day 140):
- Grade 3 or 4 AE, or
- Death (Grade 5 AE)

2.3.3 Other Objective and Outcome Measure

2.3.3.1 To investigate the relationship between infant DTG elimination and UGT1A1 genotypes.

Note: Please refer to the Pharmacology Analysis Plan for the outcome measure and main analysis specifications.

For the supplementary analysis specified in Section 5, the DTG elimination outcome measure will be:
DTG clearance (CL/F) by UGT1A1 genotype group.

2.4 Sample Size

As outlined in Protocol Section 9.4.1, a minimum of 36 and up to 108 mother-infant pairs will be enrolled in the study to achieve a target of 36 evaluable infants receiving the proposed dose of DTG for the relevant stratum. A minimum of 6 and 12 evaluable infants will be enrolled in each stratum in Cohort 1 and Cohort 2, respectively. A maximum of 36 and 72 infants may be enrolled in Cohort 1 (across strata) and Cohort 2 (across strata), respectively.

2.5 Overview of Study Monitoring

An independent SMC will review the study regularly, following policies described in the IMPAACT Network Manual of Procedures.

SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise, or as requested by the Clinical Management Committee (CMC). Refer to Protocol Section 9.5.4 for triggers for *ad hoc* SMC reviews.

The SMC will monitor study progress, quality of study conduct, and participant safety. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

3 General Considerations

The Primary Completion Date (PCD) will be defined as the date when all infants have completed the study visit after the visit when the infant permanently discontinues study drug. Since the PCD and completion of study follow-up will occur only two months apart, the Primary Analysis Report will be generated following database lock and (per IMPAACT Network Manual of Procedures Section 19.3.1) completion of the regulatory submission tables, figures, and listings package.

Separate analyses will be done for each cohort, and by stratum and overall summary statistics will be provided. If a change in a cohort/stratum dosing occurs, summary statistics for each dosing group will also be provided. In general, continuous variables will be summarized with n (total participants included in analysis), range (minimum, maximum), median, and Interquartile Range (Q1, Q3). Categorical variables will be summarized with n and percentage (excluding missing values).

3.1 Analysis Populations and Groups for the Safety Analyses

Infants in Cohort 1 will receive two single doses of DTG, added to their standard HIV-1 ARV prophylaxis. Cohort 1 is intended to generate the PK and safety data that will inform dose selection for Cohort 2 chronic DTG dosing from Entry (0-5 days of life) through Week 4 or 6 visit based on the duration of local standard ARV prophylaxis (4-6 weeks). Cohort 2 DTG dosing may be changed based on reviews of safety and PK data.

Separate analysis will be done for Cohort 1 and Cohort 2. Safety analyses will be done for the following analysis population(s).

- **Exposed to DTG (Cohorts 1 and 2)**: All infants who received at least one dose of DTG.
- **On proposed DTG dose (Cohort 2 only)**: All infants whose starting dose for chronic DTG dosing was the final dose proposed for their cohort stratum. If there is no Cohort 2 dose change, the “Cohort 2 exposed to DTG” and “Cohort 2 on proposed DTG dose” analysis populations will be the same and no tables, figures, or listings will be produced for the “Cohort 2 on proposed DTG dose” analysis population.

3.2 Safety and Tolerability Visit Windows

The infant’s date of birth is the reference date for the infant’s Schedule of Evaluations (SoE) with day of birth defined as “Day 0”, except for the visits scheduled two and seven days from the day the initial DTG dose is administered. All available safety data through Day 140 will be used for the

safety analyses. If there are any assessments after Day 140, these will be mentioned in the report and included in any relevant per participant listings.

Safety analyses will be based on safety data from required evaluations specified in the protocol and from safety assessments done as part of the infant's clinical care. In addition, safety data will include infant study visits outside of specified visit windows in the SoE. Safety and tolerability visit windows are defined below:

Table 3.1: Cohort 1 (Strata 1A, 1B, and 1C) – SoE, Safety and Tolerability Visit Windows

Study Visit	**Screening**	**Entry**	**7 Days Post Initial Dose**	**Week 4**	**Week 6**	**Week 16 or Early Study Discontinuation**
SoE Visit Window[1]	**0 – 5 days**	**0 – 5 days**	**+ 3 days**	**23 – 33 days**	**37 – 47 days**	**112 – 140 days**
Safety Visit Window	Baseline: Day 0 until prior to 1st dose of DTG		From 1st dosing of DTG through Day 15	Days 16-35	Days 36-50	Days 51-140
Tolerability Visit Window	Day 0 until 4 days post 1st dose of DTG		From 5 days post 1st dose of DTG through Day 15	N/A	N/A	N/A

1. Day 0 is defined as the infant's date of birth (DOB), and all follow-up visits are scheduled from this date except the 7 Days Post Initial Dose visit, which is scheduled seven days (+ 3 days) from the day the initial DTG dose is administered at Entry.

Table 3.2: Cohort 2 (Stratum 2A and Stratum 2B) – SoE, Safety, and Tolerability Visit Windows

Study Visit	**Screening/ Entry**	**2 Days Post Initial Dose**	**7 Days Post Initial Dose**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16 or Early Study Discontinuation**
SoE Visit Window[1]	**0 – 5 days**	**+2 days**	**+3 days**	**23 – 33 days**	**37 – 47 days**	**51 – 61 days**	**77 – 91 days**	**112 – 140 days**
Safety Visit Window	Baseline: Day 0 until prior to 1st dose of DTG	From 1st dosing of DTG through Day 7	From 1st dosing of DTG through Day 15	Days 16-35	Days 36-50	Days 51-69	Days 70-100	Days 101-140
Tolerability Visit Window	Day 0 until 1 day post 1st dose of DTG	From 2 days post 1st dose of DTG through 5 days post 1st dose of DTG	From 6 days post 1st dose of DTG through Day 15	Days 16-35	Days 36-50	N/A	N/A	N/A

1. Day 0 is defined as the infant's date of birth (DOB) and all follow-up visits are scheduled from this date except the 2 Days Post Initial Dose Visit and 7 Days Post Initial Dose Visit, which are scheduled 2 days (+2 days) and 7 days (+ 3 days) respectively from the day the initial DTG dose is administered at Entry.

3.3 Definitions

3.3.1 Baseline

For infants, the **baseline** value will be from the last assessment prior to or on the date of the first receipt of the study drug with a non-missing value. If Screening and Entry Visits are on the same day, Entry Visit is preferred for baseline. Unless otherwise stated, if baseline is missing, no derivation will be performed, and baseline will be set to missing.

For mothers, the baseline value will be from study entry.

3.3.2 Dates

The **date of last study safety assessment** will be the last clinic visit at or prior to Day 140. If the participant dies prior to Day 140 then it will be set to the death date.

The **1st dose date** and the **off-treatment date** will be the dates the infant started on DTG and permanently taken off DTG, respectively, based on the administrative forms.

3.3.3 Duration of Follow-Up and Treatment

The **duration of follow-up** in days will be ("date of last study safety assessment" – "enrollment date" + 1).

For Cohort 2, the **duration of treatment** in days will be ("off-treatment date" – "1st dose date" + 1).

4 Estimands and Estimation

The Primary PK analysis will be done by the Protocol Pharmacologists and the estimands for PK-related primary objectives are not included in this Primary SAP. See the Pharmacology Analysis Plan for more details.

This section has the estimand specifications for the non-PK primary and secondary study objectives. It includes the main analysis approach for each study objective and if applicable the sensitivity and supplementary analyses specifications.

The following definitions apply to the primary and secondary estimands tables:

Drug-related safety failure events are as follows:

- Grade 3 or 4 AE assessed as related to study drug
- Death (Grade 5 AE) assessed as related to the study drug
- Life-threatening AE assessed as related to study drug
- AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug

For the primary analysis, the AE attribution to study drug will be based on site assessment but if the SMC is consulted, the SMC's opinion will be used. A sensitivity analysis, as needed, will be done where AE attribution to study drug will be based on site assessment only.

Safety failure events are as follows:

- Grade 3 or 4 AE
- Death (Grade 5 AE)

The safety analysis populations (i.e., exposed to DTG, on proposed DTG dose) are defined in Section 3.1. All available safety data will be used for infants who were prematurely taken off DTG for any reason, including due to HIV-1 diagnosis or due to receipt of any disallowed medications. If an infant dies, all available safety data while infant is alive will be used.

In case any infant who received at least one dose of DTG is considered not safety evaluable, the infant will be excluded from the main and sensitivity safety analyses but all available data on the infant will be summarized separately.

4.1 Primary Estimands

The safety estimands listed in this subsection are for the primary objective, "To evaluate the safety and tolerability of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life."

4.1.1 Safety estimands for the Cohorts 1 and 2 "Exposed to DTG" population: Safety through 2 weeks after discontinuation of DTG

Primary Objective 1 - safety: To evaluate the safety through 2 weeks after DTG discontinuation of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life	
Estimands description	Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **drug-related safety failure event** after initiation of DTG through 2 weeks after permanent DTG discontinuation. Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **safety failure event** after initiation of DTG through 2 weeks after permanent DTG discontinuation.
Treatment	DTG liquid suspension or DTG DT added to infant's standard of care ARV prophylaxis.

Target population	Analysis set
Generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, who received DTG, added to standard of care ARV prophylaxis	All infants who received at least one dose of DTG
Variables	**Outcome measures**
Occurrence of at least one **drug-related safety failure event** after first exposure to DTG through 2 weeks after DTG permanent discontinuation. Occurrence of at least one **safety failure event** after first exposure to DTG through 2 weeks after DTG permanent discontinuation.	Outcome measures as defined by the variables

Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: • Death assessed as related to DTG and occurs while infant is on DTG or within 2 weeks after DTG discontinuation: Infant will be considered a safety failure (composite variable strategy) • Death assessed as not related to DTG and death occurs while infant is on DTG or within 2 weeks after DTG discontinuation – For drug-related safety failure analysis: all available data used to determine the variable (while-on-treatment strategy, i.e., while alive, if infant dies while on treatment; treatment policy strategy if infant dies after DTG discontinuation) – For safety failure analysis: Infant will be considered a safety failure (composite variable strategy) • Premature DTG permanent discontinuation due to an AE assessed as related to DTG: – For drug-related safety failure analysis: Infant will be considered a safety failure (composite variable strategy). – For safety failure analysis: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation due to an AE assessed as not related to DTG: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because infant is diagnosed with HIV, receives disallowed medication, or new data become available that indicate DTG should be discontinued as determined by the CMC: All available data used to determine the variable (treatment policy strategy)	**Safety evaluable participants:** - Final Analysis Report: All infants in the analysis set who have at least one safety assessment after the 1st dose of DTG are safety evaluable, i.e., an infant with completely missing safety data after initiating DTG is safety unevaluable and will be excluded from the main and the sensitivity analyses. - Regulatory Submission Report(s): All infants in the analysis set are safety evaluable. **Main analysis:** Include all safety evaluable participants. Infants who discontinue follow-up before 2 weeks after DTG permanent discontinuation will have their outcome determined based on data available until the time of study discontinuation. An infant who prematurely discontinues follow-up prior to the safety timeframe without a drug-related safety failure event (or a safety failure event) is assumed not to have any after study discontinuation, i.e., single imputation under the best case scenario.
Population-level summary measure	**Analysis approach**
Probability among infants on DTG of experiencing at least one **drug-related safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation.	Proportion of infants on DTG who experience at least one **drug-related safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation, using point

Probability among infants on DTG of experiencing at least one **safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation.	and Clopper-Pearson 90% Confidence Interval estimates. Proportion of infants on DTG who experience at least one s**afety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation, using point and Clopper-Pearson 90% Confidence Interval estimates.

Sensitivity analyses: The main analysis will use single imputation for missing data under the best case scenario. It is recognized that this approach may result to underestimating the harm of the study drug. Sensitivity analyses will be performed for safety evaluable participants following the specifications below:

- Complete case analysis: Safety evaluable participants with any missing safety data for the safety timeframe will be excluded from the analysis.
- Single imputation under the worst case scenario: For participants who are taken off-study prior to completion of the safety timeframe, use all available safety data and assume that a drug related safety failure event (or a safety failure event) occurred after the participant was taken off-study for anyone who did not have a drug-related safety failure event (or safety failure event) at the time they were taken off-study.

Supplementary Analyses

For Cohort 2 infants in the safety analysis set, a time-to-event analysis will be performed on time to drug-related safety failure event (or safety failure event) using follow-up data through 2 weeks after permanent DTG discontinuation. Follow-up will be censored at last safety assessment for infants who discontinue study follow-up prior to 2 weeks after permanent DTG discontinuation. Kaplan-Meier (KM) 90% CI estimates of proportion of infants who experience at least one drug-related safety failures event (or safety failure event) at Weeks 6 and 8 will be generated.

4.1.2 Safety estimands for the Cohort 2 "on proposed DTG dose" population: Safety through 2 weeks after discontinuation of DTG

Primary Objective 1 - safety: To evaluate the safety through 2 weeks after DTG discontinuation of proposed DTG dose administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life	
Estimands description	Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **drug-related safety failure event** after initiation of the proposed chronic dose of DTG through 2 weeks after permanent DTG discontinuation. Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **safety failure event** after initiation of the proposed chronic dose of DTG through 2 weeks after permanent DTG discontinuation.
Treatment	DTG liquid suspension or DTG DT at proposed dose, added to infant's standard of care ARV prophylaxis, administered on or before 5 days of life through Week 4 or 6 visit.

Target population	Analysis set
Generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, who receive the proposed chronic dose of DTG, added to standard of care ARV prophylaxis	All who received at least one dose of DTG
Variables	**Outcome measures**
Occurrence of at least one **drug-related safety failure event** after initiation of DTG at the proposed chronic dose through 2 weeks after permanent DTG discontinuation. Occurrence of at least one **safety failures event** after initiation of DTG at the proposed chronic dose through weeks after permanent DTG discontinuation.	Outcome measures as defined by the variables
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: • Death assessed as related to DTG and occurs while infant is on DTG or within 2 weeks after DTG discontinuation: Infant will be considered a safety failure (composite variable strategy) • Death assessed as not related to DTG and occurs while infant is on DTG or within 2 weeks after DTG discontinuation: – For drug-related safety failure analysis: all available data used to determine the variable (while-on-treatment strategy, i.e., while alive, if infant dies while on treatment; treatment policy strategy if infant dies after DTG discontinuation) - For safety failure analysis: Infant will be considered a safety failure (composite variable strategy) • Premature DTG permanent discontinuation due to an AE assessed as related to DTG: - For drug-related safety failure analysis: Infant will be considered a safety failure (composite variable strategy) - For safety failure analysis: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation due to an AE assessed as not related to DTG: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being: All available data used	**Safety evaluable participants:** <u>- Final Analysis Report</u>: All infants in the analysis set who have at least one safety assessment after the 1st dose of DTG are safety evaluable, i.e., an infant with completely missing safety data after initiating DTG is safety unevaluable and will be excluded from the main and the sensitivity analyses. <u>- Regulatory Submission Report(s):</u> All infants in the analysis set are safety evaluable. **Main analysis:** Include all safety evaluable participants. Infants who discontinue follow-up before 2 weeks after DTG permanent discontinuation will have their outcome determined based on safety data available until the time of study discontinuation. An infant who prematurely discontinues follow-up prior to the safety timeframe without a drug-related safety failure event (or a safety failure event) is assumed not to have any after study discontinuation, i.e., single imputation under the best case scenario.

to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because infant is diagnosed with HIV, receives disallowed medication, or new data become available that indicate DTG should be discontinued as determined by the CMC: All available data used to determine the variable (treatment policy strategy)	
Population-level summary measure	Analysis approach
Probability among infants on the proposed DTG dose of experiencing at least one **drug-related safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation. Probability among infants on the proposed DTG dose of experiencing at least one **safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation.	Proportion of infants on the proposed DTG dose who experience at least one **drug-related safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation, bounded by a Clopper-Pearson 90% Confidence Interval. Proportion of infants on the proposed DTG dose who experience at least one **safety failure event** after initial DTG dosing through 2 weeks after DTG permanent discontinuation, bounded by a Clopper-Pearson 90% Confidence Interval.

Sensitivity analyses: The main analysis will use single imputation for missing data under the best case scenario. It is recognized that this approach may result to underestimating the harm of the study drug. Sensitivity analyses will be performed for safety evaluable participants following the specifications below:

- Complete case analysis: Safety evaluable participants with any missing safety data for the safety timeframe will be excluded from the analysis.
- Single imputation under the worst case scenario: For participants who are taken off-study prior to completion of the safety timeframe, use all available safety data and assume that a drug related safety failure event (or a safety failure event) occurred after the participant was taken off-study for anyone who did not have a drug-related safety failure event (or safety failure event) at the time they were taken off-study.

Supplementary Analyses

For Cohort 2 infants in the safety analysis set, a time-to-event analysis will be performed on time to drug-related safety failure event (or safety failure event) using follow-up data through 2 weeks after permanent DTG discontinuation. Follow-up will be censored at last safety assessment for infants who discontinue study follow-up prior to 2 weeks after permanent DTG discontinuation. Kaplan-Meier (KM) 90% CI estimates of proportion of infants who experience at least one drug-related safety failures event (or safety failure event) at Weeks 6 and 8 will be generated.

4.1.3 Tolerability estimand for the "Exposed to DTG" population: Cohorts 1 and 2

<table>
<tr><td colspan="3">Primary Objective 1 - tolerability: To evaluate the tolerability of proposed DTG dose administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life</td></tr>
<tr><td>Estimand description</td><td colspan="2">Among generally healthy, singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks at birth and weight at birth of at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing any problems taking DTG or any AE assessed as related to study drug that leads to premature permanent discontinuation of the DTG.</td></tr>
<tr><td>Treatment</td><td colspan="2">DTG liquid suspension and DTG DT added to infant's standard of care ARV prophylaxis.</td></tr>
<tr><td>Target population</td><td colspan="2">Analysis set</td></tr>
<tr><td>Generally healthy, singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks at birth and weight at birth of at least 2 kg, less than or equal to 5 days of life at initiation of DTG, added to standard of care ARV prophylaxis</td><td colspan="2">Infants who received at least one dose of DTG.</td></tr>
<tr><td>Variable</td><td colspan="2">Outcome measure</td></tr>
<tr><td>Occurrence that an infant on DTG will experience any problems taking the study drug or any AE that leads to premature permanent discontinuation of DTG.

An infant in Cohort 1 is defined as having problems taking DTG if they refuse, vomit or spit up, gag or identify other difficulties taking any of the 2 DTG doses.

An infant in Cohort 2 is defined as having problems taking DTG if they refuse, vomit or spit up, gag or identify other difficulties taking DTG for "approximately half of the doses" or "most doses" anytime through study drug discontinuation.</td><td colspan="2">Outcome measure as defined by the variables</td></tr>
<tr><td>Handling of intercurrent events</td><td colspan="2">Handling of missing data</td></tr>
<tr><td>The following intercurrent events are relevant to the estimand:

• Death while on DTG:
- For death related to DTG: Infant will be considered a tolerability failure (composite variable strategy)
- For death not related to DTG: All available data used to determine the variable (while alive strategy)

• Premature study discontinuation while on DTG: All available data used to determine the variable (treatment policy strategy)

• Premature DTG permanent discontinuation due an AE: Infant will be considered a tolerability failure (composite variable strategy)

• Premature DTG permanent discontinuation because site investigator determines that further</td><td colspan="2">Participants included in tolerability analysis:

<u>- Final Analysis Report</u>: All infants in the analysis set who have at least one safety or tolerability assessment after the 1st dose of DTG will be included, i.e., an infant with completely missing safety <u>and</u> tolerability data after initiating DTG will be excluded from the main and the sensitivity analyses.

<u>- Regulatory Submission Report(s):</u> All infants in the analysis set are included.

Main analysis:
Include all participants who are included in tolerability analysis as specified above. Participants who have missing tolerability assessment will have their outcome determined based on available data.</td></tr>
</table>

administration of DTG would be detrimental to the infant's health or well-being: Infant will be considered a tolerability failure (composite variable strategy) • Premature DTG permanent discontinuation because infant is diagnosed with HIV, receives disallowed medication, or new data become available that indicate DTG should be discontinued as determined by the CMC: All available data used to determine the variable (treatment policy strategy)	
Population-level summary measure	Analysis approach
Probability of an infant not able to tolerate DTG.	Proportion of infants who experience any problems taking DTG or experience any AE that leads to premature permanent discontinuation of the proposed DTG dose, using point and Clopper-Pearson 90% Confidence Interval estimates.

Supplementary Analyses (Cohort 2 only)

The analysis will follow the specification above except that:

An infant in Cohort 2 is defined as having problems taking DTG if they refuse, vomit or spit up, gag or identify other difficulties taking DTG for "infrequently", "approximately half of the doses" or "most doses" anytime through study drug discontinuation (i.e., Week 4 or 6 visit).

4.1.4 Tolerability estimand for the "on proposed DTG dose" population: Cohort 2 only

Primary Objective 1 - tolerability: To evaluate the tolerability of proposed DTG dose administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life	
Estimand description	Among generally healthy, singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth of at least 2 kg, less than or equal to 5 days of life at initiation of proposed DTG dose, the probability of experiencing any problems taking DTG or any AE assessed as related to study drug that leads to premature permanent discontinuation of the DTG.
Treatment	DTG liquid suspension and DTG DT at proposed dose added to infant's standard of care ARV prophylaxis.

Target population	Analysis set
Generally healthy, singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth of at least 2 kg, less than or equal to 5 days of life at initiation of DTG added to standard of care ARV prophylaxis	All who received at least one dose of DTG
Variable	Outcome measure
Occurrence that an infant on DTG proposed dose will experience any problems taking the study drug[a] or any	Outcome measure as defined by the variables

AE that leads to premature permanent discontinuation of DTG. [a] An infant in Cohort 2 is defined as having problems taking DTG if they refuse, vomit or spit up, gag or identify other difficulties taking DTG for "approximately half of the doses" or "most doses" anytime through study drug discontinuation.	
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: • Death while on DTG: - For death related to DTG: Infant will be considered a tolerability failure (composite variable strategy) - For death not related to DTG: All available data used to determine the variable (while alive strategy) • Premature study discontinuation while on DTG: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation due an AE: Infant will be considered a tolerability failure (composite variable strategy) • Premature DTG permanent discontinuation because site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being: Infant will be considered a tolerability failure (composite variable strategy) • Premature DTG permanent discontinuation because infant is diagnosed with HIV, receives disallowed medication, or new data become available that indicate DTG should be discontinued as determined by the CMC: All available data used to determine the variable (treatment policy strategy)	**Participants included in tolerability analysis:** <u>- Final Analysis Report</u>: All infants in the analysis set who have at least one safety or tolerability assessment after the 1st dose of DTG will be included, i.e., an infant with completely missing safety <u>and</u> tolerability data after initiating DTG will be excluded from the main and the sensitivity analyses. <u>- Regulatory Submission Report(s):</u> All infants in the analysis set are included. **Main analysis:** Include all participants who are included in tolerability analysis as specified above. Participants who have missing tolerability assessment will have their outcome determined based on available data.
Population-level summary measure	Analysis approach
Probability of an infant not able to tolerate the proposed DTG dose.	Proportion of infants who have any problems taking the proposed DTG dose or experience any AE that leads to premature permanent discontinuation of the proposed DTG dose, using point and Clopper-Pearson 90% Confidence Interval estimates.

<u>Supplementary Analyses (Cohort 2 only)</u>

The analysis will follow the specification above except that:

An infant in Cohort 2 is defined as having problems taking DTG if they refuse, vomit or spit up, gag or identify other difficulties taking DTG for "infrequently", "approximately half of the doses" or "most doses" anytime through study drug discontinuation.

4.2 Secondary Estimands

The safety estimands listed in this subsection are for the secondary objective, "To evaluate the safety of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first 16 weeks of life."

4.2.1 Safety estimands for Cohorts 1 and 2 "Exposed to DTG" population: Safety through Week 16

Secondary Objective 1: To evaluate the safety through Week 16 of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in first four to six weeks of life	
Estimands description	Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **drug-related safety failure event** after initiation of DTG through Week 16 (Day 140). Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one **safety failure event** after initiation of DTG through Week 16 (Day 140).
Treatment	DTG liquid suspension and DTG DT, added to infant's standard of care ARV prophylaxis.

Target population	Analysis set
Generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, who receive the DTG, added to standard of care ARV prophylaxis	All who received at least one dose of DTG
Variables	**Outcome measures**
Occurrence of at least one **drug-related safety failures event** after first exposure to DTG through Week 16 (Day 140). Occurrence of at least one **safety failures event** after first exposure to DTG through Week 16 (Day 140).	Outcome measures as defined by the variables
Handling of intercurrent events	**Handling of missing data**
The following intercurrent events are relevant to the estimand: • Death assessed as related to DTG and occurs after initiation of DTG to Week 16 (Day 140): Infant will be considered a safety failure (composite variable strategy) • Death assessed as not related to DTG and death occurs after initiation of DTG to Week 16 (Day 140): – For drug-related safety failure analysis: all available data used to determine the variable (while-on-	**Safety evaluable participants:** <u>- Final Analysis Report</u>: All infants in the analysis set who have at least one safety assessment after the 1st dose of DTG are safety evaluable, i.e., an infant with completely missing safety data after initiating DTG is safety unevaluable and will be excluded from the main and the sensitivity analyses.

treatment strategy, i.e., while alive, if infant dies while on treatment; treatment policy strategy if infant dies after DTG discontinuation) – For safety failure analysis: Infant will be considered a safety failure (composite variable strategy) • Premature DTG permanent discontinuation due to an AE assessed as related to DTG: - For drug-related safety failure analysis: Infant will be considered a safety failure (composite variable strategy) - For safety failure analysis: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation due to an AE assessed as not related to DTG: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because infant is diagnosed with HIV, receives disallowed medication, or new data become available that indicate DTG should be discontinued as determined by the CMC: All available data used to determine the variable (treatment policy strategy)	- Regulatory Submission Report(s): All infants in the analysis set are safety evaluable. **Main analysis:** Include all safety evaluable participants. Infants who discontinue follow-up before Week 16 (Day 140) will have their outcome determined based on data available until the time of discontinuation. An infant who prematurely discontinues follow-up prior to the safety timeframe without a drug-related safety failure event (or a safety failure event) is assumed not to have any after study discontinuation, i.e., single imputation under the best case scenario.
Population-level summary measure	**Analysis approach**
Probability among infants on DTG who experiencing at least one **drug-related safety failure event** after initial DTG through Week 16 (Day 140).	Proportion of infants on DTG who experience at least one **drug-related safety failure event** after initial DTG dosing through Week 16 (Day 140), using point and Clopper-Pearson 90% Confidence Interval estimates.
Probability among infants on DTG who experiencing at least one **safety failure event** after initial DTG dosing through Week 16 (Day 140).	Proportion of infants on DTG who experience at least one **safety failure event** after initial DTG dosing through Week 16 (Day 140), using point and Clopper-Pearson 90% Confidence Interval estimates.

Sensitivity analyses: The main analysis will use single imputation for missing data under the best case scenario. It is recognized that this approach may result to underestimating the harm of the study drug. Sensitivity analyses will be performed for safety evaluable participants following the specifications below:

- Complete case analysis: Safety evaluable participants with any missing safety data will be excluded from the analysis.

- Single imputation under the worst case scenario: For participants who are taken off-study prior to completion of the safety timeframe, use all available safety data and assume that a drug related safety failure event (or a safety failure event) occurred after the participant was taken off-study for anyone who did not have a drug-related safety failure event (or safety failure event) at the time they were taken off-study.

Supplementary Analyses

For Cohort 2 infants in the safety analysis set, a time-to-event analysis will be performed on time to drug-related event (or safety failure event) using follow-up data through Week 16 (Day 140). Follow-up will be censored at last safety assessment for infants who discontinue study follow-up prior to Week 16. KM 90% CI estimates of proportion of infants who experience at least one drug-related safety failure event (or safety failure event) at Weeks 4, 6, 8, and 16 will be generated.

4.2.2 Safety estimands for the Cohort 2 "on proposed DTG dose" population: Safety through Week 16

<table>
<tr><td colspan="3">Secondary Objective 1: To evaluate the safety through Week 16 of proposed DTG dose administered to HIV-1-exposed infants with standard ARV prophylaxis in first four to six weeks of life</td></tr>
<tr><td>Estimand description</td><td colspan="2">Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, the probability of experiencing at least one drug-related safety failure event after initiation of the proposed chronic dose of DTG through Week 16 (Day 140).

Among generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of the proposed chronic dose of DTG, the probability of experiencing at least one safety failure event after initiation of DTG through Week 16 (Day 140).</td></tr>
<tr><td>Treatment</td><td colspan="2">DTG liquid suspension and DTG DT at proposed dose, added to infant's standard of care ARV prophylaxis, administered on or before 5 days of life through Week 4 or 6 visit.</td></tr>
<tr><td colspan="2">Target population</td><td>Analysis set</td></tr>
<tr><td colspan="2">Generally healthy singleton infants born to mothers living with HIV-1, with gestational age of at least 37 weeks and weight at birth at least 2 kg, less than or equal to 5 days of life at initiation of DTG, who receive the proposed chronic dose of DTG, added to standard of care ARV prophylaxis</td><td>All who received at least one dose of DTG</td></tr>
<tr><td colspan="2">Variables</td><td>Outcome measures</td></tr>
<tr><td colspan="2">Occurrence of at least one drug-related safety failure event after initiation of DTG at the proposed chronic dose through Week 16 (Day 140).

Occurrence of at least one safety failures event after initiation of DTG at the proposed chronic dose through Week 16 (Day 140).</td><td>Outcome measures as defined by the variables</td></tr>
<tr><td colspan="2">Handling of intercurrent events</td><td>Handling of missing data</td></tr>
</table>

The following intercurrent events are relevant to the estimand: • Death assessed as related to DTG and occurs after initiation of DTG at proposed chronic dose through Week 16 (Day 140): Infant will be considered a safety failure (composite variable strategy) • Death assessed as not related to DTG and occurs after initiation of DTG at proposed chronic dose through Week 16 (Day 140): – For drug-related safety failure analysis: all available data used to determine the variable (while-on-treatment strategy, i.e., while alive, if infant dies while on treatment; treatment policy strategy if infant dies after DTG discontinuation) – For safety failure analysis: Infant will be considered a safety failure (composite variable strategy) • Premature DTG permanent discontinuation due to an AE assessed as related to DTG: – - For drug-related safety failure analysis: Infant will be considered a safety failure (composite variable strategy) – - For safety failure analysis: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation due to an AE assessed as not related to DTG: All available data used to determine the variable (treatment policy strategy) • Premature DTG permanent discontinuation because site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being: All available data used to determine the variable (treatment policy strategy)	**Safety evaluable participants:** <u>- Final Analysis Report</u>: All infants in the analysis set who have at least one safety assessment after the 1st dose of DTG are safety evaluable, i.e., an infant with completely missing safety data after initiating DTG is safety unevaluable and will be excluded from the main and the sensitivity analyses. <u>- Regulatory Submission Report(s):</u> All infants in the analysis set are safety evaluable. **Main analysis:** Include all safety evaluable participants. Infants who discontinue follow-up before Week 16 (Day 140) will have their outcome determined based on data available until the time of discontinuation. An infant who prematurely discontinues follow-up prior to the safety timeframe without a drug-related safety failure event (or a safety failure event) is assumed not to have any after study discontinuation, i.e., single imputation under the best case scenario.
Population-level summary measure	Analysis approach
Probability among infants on the proposed DTG dose of experiencing at least one **drug-related safety failure event** after initial DTG through Week 16 (Day 140). Probability among infants on the proposed DTG dose of experiencing least one **safety failure event** after initial DTG dosing through Week 16 (Day 140).	Proportion of infants on the proposed DTG dose who experience at least **one drug-related safety failure event** after initial DTG dosing through Week 16 (Day 140), bounded by a Clopper-Pearson 90% Confidence Interval. Proportion of infants on the proposed DTG dose who experience at least one **safety failure event** after initial DTG dosing through Week 16 (Day 140), bounded by a Clopper-Pearson 90% Confidence Interval.

<u>Sensitivity analyses:</u> The main analysis will use single imputation for missing data under the best case scenario. It is recognized that this approach may result to underestimating the harm of the

study drug. Sensitivity analyses will be performed for safety evaluable participants following the specifications below:

- Complete case analysis: Safety evaluable participants in the analysis set with any missing safety data for the safety timeframe will be excluded from the analysis.
- Single imputation under the worst case scenario: For participants who are taken off-study prior to completion of the safety timeframe, use all available safety data and assume that a drug related safety failure event (or a safety failure event) occurred after the participant was taken off-study for anyone who did not have a drug-related safety failure event (or safety failure event) at the time they were taken off-study.

Supplementary Analyses

For Cohort 2 infants in the safety analysis set, a time-to-event analysis will be performed on time to drug-related safety failure event (or safety failure event) using follow-up data through 2 weeks after permanent DTG discontinuation. Follow-up will be censored at last safety assessment for infants who discontinue study follow-up prior to 2 weeks after permanent DTG discontinuation. Kaplan-Meier (KM) 90% CI estimates of proportion of infants who experience at least one drug-related safety failures event (or safety failure event) at Weeks 6 and 8 will be generated.

5 Analysis of Other Objectives

Objective: To investigate the relationship between infant DTG elimination and UGT1A1 genotypes.

Intensive PK sampling times for Cohort 1 are at entry and 7 days post initial dose. Intensive PK sampling times for Cohort 2 are at 7 days post initial dose and Week 4. Genotype sampling is optional and can be done at any visit.

The primary analysis for the study objective will be done by the Protocol Pharmacologists and will be described in the Pharmacology Analysis Plan. The statisticians will perform Supplementary Analysis described below.

The analysis will be done by cohort at each intensive PK sampling visit within the cohort. Only infants with non-missing DTG clearance (CL/F) and UGT1A1 genotype data will be included in the analysis. DTG CL/F will be summarized (i.e., n, median, IQR, range, mean, standard deviation will be provided) by UGT1A1 genotype group. The median CL/F between UGT1A1 genotype groups will be compared using Wilcoxon Rank-Sum test or Kruskal-Wallis test at $\alpha=0.05$. The power of the test will depend upon the number of genotype groups being compared and the distributions of the variables to be analyzed and will be extremely limited if the sample size is small.

If death or DTG permanent discontinuation happens before the PK sampling visit, DTG CL/F will be unavailable. If death happens before sampling for UGT1A1

genotyping, UGT1A1 genotype data will be unavailable. Any infant with unavailable DTG CL/F or UGT1A1 genotype data will be excluded from the analysis (complete case analysis).

To summarize the extent of the missing data, the following will be provided:

- n and % for DTG CL/F data by cohort at each intensive sampling visit using the following categories: Non-missing data, intensive PK sampling was not done, PK sampling done but DTG CL/F is not available.
- n and % for UGT1A1 data by cohort using the following categories: Non-missing data, genotypic sampling was not done, genotypic sampling done but UGT1A1 genotype data is not available.

6 Other Analyses

Maternal medical history, maternal ARVs during pregnancy and at the Entry visit, duration of infant DTG, infant's standard of care ARVs, and infant's receipt of breast milk may be relevant for the interpretation of safety and PK data. Listings and summary tables will be generated. Specifications for these analyses will be in the AIP.

In addition to the analyses of the safety outcome measures specified in Section 5, the proportion of infants who have at least (i) one AE related to DTG, (ii) one AE which leads to temporary/premature permanent DTG discontinuation and (iii) one SAE will be provided. Per participant line listings of drug-related safety failure events, AEs related to DTG, AEs which lead to temporary/premature permanent DTG discontinuation, SAEs, and AEs reviewed by the SMC will be generated. In case there is any discrepancy between site assessment and SMC opinion of AE attribution to DTG, sensitivity analyses will be done.

Summaries of worst grade AEs by MedDRA Preferred Term (PT) grouped by System Organ Class (SOC) will be generated for all AEs.

- Cohort 1: Summary tables will be generated using safety data through Week 16.
- Cohort 2: Summary tables will be generated using safety data through two weeks after permanent discontinuation of DTG and through Week 16.

7 Report Contents for Final Analysis Reports

This section provides a general overview of the contents which will be in the Final Analysis Reports. Analysis details will be provided in the AIP.

- CONSORT diagram
- Accrual
- Demographics and baseline characteristics (reported in ClinicalTrials.gov)
  - Maternal demographic and baseline: race, ethnicity, age at entry, last DTG dose prior to delivery (days before delivery)
  - Infant demographic and baseline: sex, race, ethnicity, gestational age at birth, birth weight, breast feeding status or intent to breastfeed
- Study status (reported in ClinicalTrials.gov)

  - Off-study reason
  - Duration of follow-up
- Treatment status
  - Study treatment permanent discontinuation reasons
  - Temporarily treatment hold reasons (Cohort 2)
  - Receipt of 1st and 2nd DTG doses (Cohort 1)
  - Duration of treatment (Cohort 2)
- Infant HIV infection status
- Analysis of primary outcome measures (reported in ClinicalTrials.gov)
  - Primary safety analysis
  - Primary tolerability analysis
- Analysis of secondary outcome measures (reported in ClinicalTrials.gov)
  - Secondary safety analysis
- Analysis of other outcome measure
- Other Analyses

Note: For each estimand in the Primary SAP, summaries of the number and timing of each intercurrent event in each treatment group will be provided.

8 Associated Documents

Note: As a regulatory submission study, the timetable for the IMPAACT 2023 Primary Analysis Report will differ substantially from the usual IMPAACT timetable due to (1) shortened timelines for data submission, QC, and database freeze/lock, and (2) generation of the regulatory submission deliverables first, followed by the Primary Analysis Report. Consequently, timetables for the regulatory submission deliverables and the Primary Analysis Report will be provided separately.

Attachment 1: Writing Team Roster