IMPAACT P1110

A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-1-EXPOSED NEONATES AT HIGH RISK OF ACQUIRING HIV-1 INFECTION

DAIDS Study ID # 11891
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ClinicalTrials.gov ID: NCT01780831

STATISTICAL ANALYSIS PLAN
Version 3.0

This is IMPAACT P1110 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted

Due to the fact that there was no hyperbilirubinemia in the study population, the objectives related to hyperbilirubinemia included in section 4.9 of the SAP was not pursued.

January 3, 2017

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DOCUMENT ADMINISTRATION

General Information		
Protocol Document Definition		IMPAACT P1110 Statistical Analysis Plan Version 3.0, January 3, 2017
Related Documents		IMPAACT P1110 (DAIDS Document ID 11891) A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at High Risk of Acquiring HIV-1 Infection, International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group, Final Version 1.0, Date: 10 December 2012 Letter of Amendment #1 dated 22 April 2014 for: P1110 Version 1.0 Letter of Amendment #2 dated 30 June 2015 for: P1110 Version 1.0 Letter of Amendment #3 dated 18 May 2016 for: P1110 Version 1.0 Clarification Memo #1 dated 1 April 2014 for: P1110 Version 1.0 Clarification Memo #2 dated 16 September 2014 for: P1110 Version 1.0 Clarification Memo #3 dated 15 January 2015 for: P1110 Version 1.0 Clarification Memo #4 dated 8 May 2015 for: P1110 Version 1.0 IMPAACT P1110 Monitoring Plan dated 14 April 2014 for: P1110 Version 1.0
Document Owner		**SDAC/HSPH**
Version History		
Date	**Version**	**Note of updates**
12 February 2015	V1.0	Analysis for Cohort 1 (with no RAL-exposed infants)
01 July 2015	V2.0	Additional summary statistics added to account for subgroups of infants within Cohorts 1 and 2 and in utero RAL exposure.

January 3, 2017	V3.0	• Specified that two final analysis reports will be generated:
		  o For protocol Version 1.0: A report focusing on Cohort 1 (both RAL naïve and exposed groups) and Cohort 2 RAL naïve group
		  o In the event that protocol Version 2.0 is approved: A report focusing on Cohort 2 (both RAL naïve and exposed groups)
		• Added the definition of wide analysis visit windows
		• Added summary tables:
		  o Study treatment status
		  o Age at 1st RAL dose for Cohort 2 infants
		  o Summary of worst grade baseline events
		• Added a section on Cohort 2 adherence to RAL
		• Modified the summary tables for summarizing infant infection status
		• Clarified that Adverse Events (AEs) and Suspected Adverse Drug Reactions (SADRs) exclude events assessed by the team as "baseline" or "ongoing baseline"
		• Clarified the definition of primary and secondary safety endpoints
		• Added infant listings which will be used internally at SDAC in writing the SDAC final analysis report and will be provided to the manuscript writing team
		• Removed analysis for CL/F among SLCO1B3 genotypes.
		• Added the definition of wild-type vs. mutation for UGT1A1 and SLCO1B3 genotypes
		• Added mock-up tables for CL/F analysis between different genotypes of UGT1A1
		• Added mock-up tables for Hyperbilirubinemia analysis among different genotypes of UGT1A1 and SLCO1B3
		• Updated team roster

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1 Purpose of the Analysis Plan

This Analysis Plan outlines the components of the primary data analysis for IMPAACT P1110. The focus is on analyses of administrative, baseline and safety data, analyses needed to address the study's primary and secondary objectives, and the analyses to assess whether safety guidelines have been met at interim and final accrual to Cohorts 1 and 2. This document focuses on analyses necessary for scientific purposes; any additional analyses needed for the regulatory purposes of the pharmaceutical sponsor will be specified in a separate document. The procedures and reports involved with protocol team monitoring of safety data during regular team calls are not fully described in this document (see the Study Monitoring Plan for details concerning monitoring). The pharmacology data will be analyzed separately by the protocol pharmacologist. The purpose of this analysis plan is:

- to ensure that the protocol team is aware of all the major issues that will be in the proposed analyses, and agrees on the contents of these analyses; and
- to specify how we intend to investigate the study questions listed in the protocol objectives and the way that data are to be analyzed and presented.

This analysis plan, therefore, includes the key analyses which might lead to modification or termination of the study and which also form the core of any presentation or publication used to disseminate the primary conclusions of the study. It is, however, recognized that this analysis plan may be modified by the core study team as new information becomes available outside of the study, or to reflect recommendations made by the Study Monitoring Committee (SMC).

2 Protocol Overview

This is a Phase I multi-center, open label, non-comparative study to evaluate the safety and pharmacokinetics (PK) of raltegravir (RAL) administered to HIV-1-exposed full-term (≥37 weeks of gestation) neonates at high risk of acquiring HIV-1 infection. The goal is to determine the appropriate dosing regimen of RAL oral granules for suspension that can be safely administered to neonates and infants in the first 6 weeks of life.

This study will enroll approximately 50 neonates in order to accrue a minimum of 32 PK evaluable high risk HIV-1-exposed neonates and their mothers across Cohort 1 and Cohort 2. Mother-infant (M-I) pairs will enroll at the time of delivery up to 48 hours of life, which is the latest time for administration of first neonatal RAL dose. Cohort 1 opened first and accrual to Cohort 2 was contingent upon neonates enrolled in Cohort 1 successfully meeting safety criteria and providing adequate PK data so that the dosing regimen was developed for daily dosing through 6 weeks of age for Cohort 2. Through Protocol Version 1.0 LoA #2 Cohort 2 RAL-naïve group was opened to accrual with the following dosage: 1.5 mg/kg once daily during Days 1-7 of life, 3.0 mg/kg twice daily during Days 8-28 of life, and 6.0 mg/kg twice daily during Days 29-42 of life.

At the time of this SAP update, Cohort 1 (both RAL-naïve and RAL-exposed groups) is closed to accrual and follow-up and Cohort 2 RAL-naïve group is closed to accrual but follow-up is ongoing. The final accrual numbers are 10 M-I pairs for Cohort 1 RAL-naïve, 6 M-I pairs for Cohort 1 RAL-exposed, and 26 M-I pairs for Cohort 2 RAL-naïve groups under protocol Version 1.0. The team estimated that the study will take 3 years to fully accrue under protocol

Version 1.0. Protocol Version 2.0 is currently being drafted and if approved, will open accrual to Cohort 2 RAL exposed group.

PK evaluable infants are those whose PK results provide data on the primary PK parameters of interest. If a participant has unevaluable PK data, which reflects uncertainty about appropriate exposure to the study medication, the participant will be excluded from PK analyses and will be replaced. PK analyses will be done by the protocol pharmacologist.

Safety data will include death, signs/symptoms, diagnoses and laboratory test results, which will include results of evaluations specified in the protocol and results from the infant's clinical care. Infants will be evaluable for safety analysis if they received at least one dose of RAL. The safety analyses for the final SDAC reports will be based on data on all safety evaluable infants, regardless of whether they are evaluable for PK analysis.

Under protocol Version 1.0, the following describes the safety monitoring for dose finding purposes:

- the team will monitor RAL safety during the regular team monitoring as specified in Protocol Section 8.52; and
- the assessment of the safety guidelines will be performed at full accrual to Cohort 1 (Protocol Section 8.521), at interim analysis when 8 participants have been accrued to Cohort 2 RAL-naïve group (Protocol Section 8.522) and at full accrual to Cohort 2 RAL-naïve group (Protocol Section 8.523).

For dose finding purposes, infants who have been excluded from the PK analyses due to evidence of problematic exposure to the study medication, will also be excluded from evaluation of the safety guidelines.

Infants will be followed for 24 weeks after birth. Women will be followed until discharge from the labor and delivery unit.

PRIMARY OBJECTIVES:

1. To evaluate the safety and tolerability through 6 weeks of life of RAL oral granules for suspension when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to HIV-1 exposed infants assessed at high risk of HIV infection.

2. To evaluate the PK of RAL oral granules for suspension during the first 6 weeks of life along with standard PMTCT ARV prophylaxis.

3. To determine an appropriate dose of RAL oral granules for suspension for use in neonates and infants during the first 6 weeks of life.

SECONDARY OBJECTIVES:

1. To assess safety and tolerability of RAL oral granules for suspension through 24 weeks of life when administered during the first 6 weeks of life with standard PMTCT ARV prophylaxis to HIV-1 exposed infants assessed at high risk of HIV infection.

2. To investigate the relationship between neonatal RAL elimination and UGT1A1 genotype, and to determine whether there is an association of UGT1A1 (**28/*28*) and SLCO1B3 (rs2117032-C/T) with hyperbilirubinemia.

3 Protocol Team Roster

4 Outline of Planned Analysis

This section contains the details of the analyses for:

- interim and full cohort accrual safety reports: at full accrual to Cohort 1, at interim analysis when 8 participants have been accrued to Cohort 2 (safety analysis only) and at full accrual to Cohort 2 RAL-naïve group; and
- SDAC final reports: the first report will focus on Cohort 1 (both RAL naïve and exposed groups) and Cohort 2 RAL naïve group. Should protocol Version 2.0 be approved and Cohort 2 RAL-exposed group be opened to accrual, a second report will be generated at study closure to follow-up for Cohort 2 (both RAL naïve and exposed groups).

When applicable, separate summary tables will be generated for the women and their infants. Separate summary tables will be generated for each cohort since Cohort 1 neonates will receive two single RAL dosing while Cohort 2 neonates will receive daily RAL dosing through 6 weeks of life. Summary statistics for subgroups of infants will be provided alongside the overall cohort summary statistics. Infant subgroups will be defined in terms of infant in utero RAL exposure and RAL dosing. For Cohort 1, there are 3 infant subgroups: (i) RAL-naïve (3mg/kg-3mg/kg), (ii) RAL-naïve (2mg/kg-3mg/kg), and (iii) RAL-exposed (1.5mg/kg-3mg/kg). Cohort 2 RAL-naïve group only has one dosing which was specified in **Section 2**.

The interim and full cohort accrual safety reports will be prepared for the core team and, if necessary, for the SMC. These reports will include information concerning Screening and Entry, Participant and Study Status, Baseline, and Safety summary tables. Unless otherwise noted the SDAC final reports will contain all summary tables.

Additional participant listings necessary in writing up the SDAC final report will be generated and will be used internally at SDAC. Highlights of these listings will be included in the SDAC final report. These participant listings will be provided to the manuscript writing team. The manuscript writing team, which is a subset of the protocol team, will be identified by the protocol team.

The analysis of the PK data will be performed by the protocol pharmacologists and thus, not included in this document.

Validation requirements as per SDAC SOPs will be as follows:

a. All dataset creation programs will be validated with double coding for the primary and secondary safety endpoints.
b. All study-specific formats will be validated.
c. Validation of analysis programs is specified in the following subsections.

4.1 Screening and Entry

Purpose:
To give a summary of the accrual progress of the study during interim analyses and final analysis.

Analysis Program Validation:
Not required.

Data:
Date and institution of enrollment and eligibility status will be from the STATUS table; comments related to eligibility deviations will be from COMENT table. Safety analysis exclusions will be from STUDMONR table and ADM0021 (first dose date); PK analysis exclusion will be from STUDMONR table; comments related to PK exclusion will be from STUMONR and COMENT tables. Reasons for screening failures and non-enrollment will be from the SCR0029 CRF.

Analysis:

4.1.1 Accrual

a) Mother-infant pair accrual:
   i. Accrual by month and by site
   ii. Total accrual

b) Infants
   i. Birth by month
   ii. Total infants accrued (Overall and by infant subgroup)

c) Screening failures and non-enrollment
   Table: Total number of M-I pairs who did not enroll
   Table: Reasons mother did not enroll
   Table: Reasons infant did not enroll

4.1.2 Eligibility Violations and Analysis Exclusions

Table: Listing of M-I pairs eligibility criteria violations and analysis exclusions which will include (i) enrolling site; (ii) reason for eligibility violation or analysis exclusions; and (iii) team decision on whether to include the M-I pair in the safety/PK analyses; (iiii) infant subgroup information

Table 1: Eligibility Violation and Analysis Exclusion Example

Count	Enrolling site	Participant	In Utero RAL Exposure	RAL dosing	Reason	Eligibility Violation	Safety Analysis Status	PK Analysis Status
1	XXX	MOTHER	N/A	N/A	XXX	Yes	N/A	N/A
		CHILD 1	Yes	XXX	XXX	Yes	Include	Include
2	YYY	MOTHER	N/A	N/A	YYY	No	N/A	N/A
		CHILD 1	No	XXX	YYY	No	Include	Exclude

4.2 Baseline Characteristics

Purpose:
To describe maternal and infant baseline characteristics (demographic, health status and other key parameters).

Analysis Program Validation:

Not required, but code review is recommended.

Data:
The following are the CRFs/tables for this section:

- Infant and maternal demographic data: STATUS table
- Timing of enrollment: STATUS table, EVW0252
- Mode of delivery: EVW0252
- Infant birth outcome: EVW0252
- Gestational age at birth: EVW0252, PE5896
- Infant birth weight and length: PE5896
- APGAR score at 1 minute: PE5896

Analysis:

a) For mothers:
   - Age (years): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Race/ethnicity (used in the eligibility screening): N (%) by category
   - Timing of enrollment (before or after delivery)

b) For infants:
   - Gender: N (%) by category
   - Race/ethnicity: N (%) by category
   - Birth outcome: N (%) by category
   - Mode of delivery: N (%) by category
   - Gestational age at birth: N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Birth weight (gram): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - Birth length (cm): N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation
   - APGAR score at 1 minute: N, N missing, median, 25th and 75th percentiles, min, max, (if data have a reasonably normal distribution, mean and standard deviation will also be presented).
   - Age (hours) at 1st RAL dose for Cohort 2 infants: N, N missing, median, 25th and 75th percentiles, min, max, mean, standard deviation

c) Baseline Summaries:
   - When appropriate, three sets of baseline characteristics summary tables will be generated for: (i) overall enrollments, (ii) safety evaluable participants and (iii) PK evaluable participants. Infant summary tables will include summary statistics for each subgroups and overall.

Table 2: Cohort 1 Infant Baseline Characteristics (mock-up table)

Characteristics		RAL-naïve			RAL-exposed	Cohort Overall
		3mg/kg-3mg/kg	2mg/kg- 3mg/kg	Overall	1.5mg/kg-3mg/kg	
Gender	F	N (%)	N (%)	N (%)	N (%)	N (%)
	M	N (%)	N (%)	N (%)	N (%)	N (%)

Note: Additional variables will be added. Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 subgroups of infants.

4.3 Participant and Study Status

Purpose:
To describe maternal and infant study status, including whether they are on study, and whether they are evaluable for analysis for both Cohort 1 and Cohort 2 infants, to summarize RAL adherence, and to summarize tolerability for Cohort 2 infants.

Analysis Program Validation:
Not required.

Data:
Mother and infant study status will be from PSTAT in CASE table. Reasons for off-study for mothers and infants will be from OFFST in F1601 CRF. Accrued and safety/PK evaluable infants information will be from STATUS, STUDMONR, COMENT tables and ADM0021 CRF. Duration of RAL while on study is from derived ARV dataset ARV2. Off-RAL reason will be from STATUS table (RSOFFRX from PE4005).

Analysis:

a) Study Status of the Mothers and the Infants.
   Table: Reasons for off-study for mothers
   Table: Reasons for off-study for infants

b) Treatment Status of the Infants.
   Table: Reasons for off-treatment for infants

c) Timing of 1st RAL Dosing for the Infants in Cohort 2
   Table: Summary statistics for age (hours) for 1st RAL dosing for Cohort 2 infants

d) Number of Infants Accrued and Evaluable for PK/Safety Analysis.

Table 3: Number of Cohort 1 Infants Accrued and Evaluable for PK/Safety Analysis (mock-up table)

	RAL-naive			RAL-exposed	Cohort Overall
	3mg/kg-3mg/kg	2mg/kg-3mg/kg	Overall	1.5mg/kg-3mg/kg	
Infants accrued	N	N	N	N	N
Infants evaluable for safety analysis[a]	N	N	N(column %)	N(column%)	N(column %)
Infants evaluable for PK analysis[b]	N	N	N(column %)	N(column%)	N(column %)

[a] Based on if the patient received at least one dose of RAL
[b] Based on team determination

Note: Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 subgroups of infants.

e) Reasons for analysis exclusions.

Table: Reasons for PK Analysis Exclusions

4.4 Data Completeness for Safety Data

Purpose:
To summarize data completeness according to the scheduled visits for infant safety data.

Analysis Program Validation:
Not required.

Data:
Infant observed visit data are from the following CRFs: LBW0093 (CHEMDT, CHEMOBT, HEMDT, HEMAOBT) for hematologies and liver chemistries, PE6831 (VISITDT) for signs/symptoms and PE6852 (VISITDT) for diagnoses.

Analysis:

a) Infant Safety Data Collection Schedule and Visit Windows for Cohort 1 and 2. Wide analysis visit windows which include all study visits will be used to summarize data completeness. Upper limits for study visits weeks 6 and 24 will be used to define the safety endpoints for the primary and secondary safety objectives, respectively.

Table 4: Infant Safety Data Collection Schedule for Cohort 1

Evaluation	Scheduled visits							
	Visits with windows specified in SoE	Entry (within 48 hrs of birth)	Day 3-4 of life	Dose 2 Day 7-10 of life [2]	2 weeks of life (±2 days)	6 weeks of life (± 1 week)	24 weeks of life (± 4 weeks)	After 24 weeks[3]
	Wide analysis window	Days 1 and 2 of life	Days 3-6 of life	Days 7-11of life	Days 12-22 of life	Days 23-49 of life	50-196 days of life	≥197 days of life[3]
Hematologies and liver chemistries (LBW0093)		X	X[1]	X	X	X	X	
Signs and Symptoms (PE6831)		X	X	X	X	X	X	
Diagnoses (PE6852)		X	X	X	X	X	X	

[1] Only total and direct bilirubin required.
[2] Pre-dose.
[3] For safety evaluations done beyond the study specified follow-up for the neonates

Table 5: Infant Safety Data Collection Schedule for Cohort 2

Evaluation	Scheduled visits									
	Visits with windows specified in SoE	Entry (within 48 hrs of birth)	After second dose (2-4 days of life)	Day 6-9 of life	Day 15-18 of life	Day 28-32 of life	5-6 weeks of life	8-10 weeks of life (± 1 weeks)	24 weeks of life(± 4 weeks)	After 24 weeks[2]
	Wide analysis window	Days 1 and 2 of life	Days 3-5 of life	Days 6-11 of life	Days 12-23 of life	Days 24-33of life	Days 34-49 of life	Days 50-84 of life	≥85 days of life	≥197 days of life[2]
Hematologies and liver chemistries (LBW0093)		X	X[1]	X	X	X	X	X	X	
Signs and Symptoms (PE6831)		X	X	X	X	X	X	X	X	
Diagnoses (PE6852)		X	X	X	X	X	X	X	X	

[1] Only total and direct bilirubin required.
[2] For safety evaluations done beyond the study specified follow-up for the neonates

b) Data Completeness Summaries of Infant Safety Data

Table: Frequency of infant expected and observed clinic visits with completed forms of IMPAACT P1097/P1110 Hematologies and Liver Chemistries (LBW0093), Signs/Symptoms (PE6831), and Diagnoses (PE6852).

4.5 RAL Adherence for Cohort 2 Infants

Purpose:
To summarize how compliant Cohort 2 infants were with study treatment. Adherence for Cohort 1 infants will be checked, but no summary table will be generated.

Analysis Program Validation:
Code review required.

Data:
Calculation of expected number of days on RAL will use data from the STATUS table (BIRTHDT, OFFSTDT and DOSE1DT). Calculation of actual number of days on RAL will use the data from TXW0276. Off-RAL reason will be from TXW0276 (RAL1RS AND RAL2RS).

Analysis:
Cohort 2 RAL adherence will be calculated using the following equation:

$$\%\ of\ days\ on\ RAL = \frac{actual\ number\ of\ days\ on\ RAL}{expected\ number\ of\ days\ on\ RAL}\ x\ 100\%$$

Note: "expected number of days on RAL" will consider the off-study date.

Table: Summary statistics of % of days on RAL.
Table: Summary of reasons of permanent discontinuation and temporary holds of RAL.

4.6 Safety Analysis for SDAC Final Reports

Purpose:
To list the endpoints and tables of primary and secondary safety analyses for the SDAC final reports.

Analysis Program Validation:
Code review required. Primary analysis for primary safety endpoints will require double coding.

Data:
Infant safety data are adverse clinical and laboratory events reported on the following CRFs: Hematology and Liver Chemistries (LBW0093), Signs/Symptoms (PE6831), Diagnosis (PE6852) and Death (PE1414). (The following variables in the SDAC SAS datasets will be used: EVENTDSC, EVNGRDE, FORMNM and FORMTYP in EVENTS table; and TBILCV, BILPHOTO, BILTRANS, BILOTH and BILOTHSP in LBW0093).

Analysis:
There will be two final SDAC reports. The first report will focus on Cohort 1(both RAL-naïve and exposed groups) and Cohort 2 RAL-naïve group. The second report will include Cohort 2 (both RAL-naïve and exposed groups). The safety analyses will include all infants who have had at least one dose of RAL. For Cohort 2, if there was dose adjustment after the interim analysis, a sensitivity analysis will be performed on infants who were enrolled after dose adjustment and only took the adjusted dose. Adverse Events (AEs) and Suspected Adverse Drug Reactions (SADRs) will exclude events classified by the team as "baseline" or "ongoing baseline" events.

- Safety endpoints for Cohorts 1 and 2 in SDAC final reports
    - Primary safety endpoint for the final analysis:
        - Adverse events of Grade 3 or 4 severity in the EVENTS table or death reported in the Death CRF with onset date at or after study entry through 6 weeks (i.e. through 49 days of age) of life
    - Secondary safety endpoints for the final analysis:
        - Adverse events of Grade 3 or 4 severity in the EVENTS table or death reported in the Death CRF with onset date at or after study entry through 24 weeks of life (through 196 days of age)
        - Suspected adverse drug reaction (SADR*) of Grade 3 or 4 severity or death with onset date at or after study entry through 6 weeks (through 49 days of age) of life
        - Suspected adverse drug reaction (SADR*) of Grade 3 or 4 severity or death with onset date at or after study entry through 24 weeks of life (i.e. through 196 days of age)

  * For the SDAC final report, SADRs will include the following attribution to drug: 11 – "Definitely related"; 12 – "Probably related"; and 13 – "Possibly related".

- Summary tables for Cohorts 1 and 2 in the SDAC final reports (Analysis for primary and

secondary safety endpoints for final analysis)

Note: Summary tables will include statistics for infant subgroups and overall and listing will include information on infant in utero RAL exposure and RAL dosing.

Table: Summary tables showing number (%) and the 2-sided 90% confidence interval (CI) using the Clopper-Pearson exact method estimates of the proportion of infants meeting the primary and secondary safety endpoints(will provide as footnote number of infants with missing data). The primary analysis will be on the primary safety endpoint.

Table 6: Proportion of Infants Meeting the Primary Safety Endpoint (mock-up table)

RAL-naïve			RAL-exposed	Overall
3mg/kg-3mg/kg	**2mg/kg- 3mg/kg**	**Overall**	**1.5mg/kg-3mg/kg**	
N (%) [90% CI]	N (%) [90% CI]	N (%) [90% CI]	N (%) [90% CI]	N (%) [90% CI]

Note: Similar table will be generated for Cohort 2 with appropriate column labels appropriate for Cohort 2 subgroups of infants.

Table: Summary tables of worst adverse events (laboratory, signs/symptoms and diagnoses) for each of the primary and secondary safety endpoint.

Table: Summary of worst grade baseline events (laboratory, signs/symptoms and diagnoses).

Table: Listing of reasons for infant death and age (weeks) at death.

Table: Summary table showing number (%) and the 2-sided 90% confidence interval (CI) using the Clopper-Pearson exact method estimates of the proportion of infants who had total bilirubin exceeding 16.0 mg/dL, or received phototherapy, transfusion therapy or other therapies for hyperbilirubinemia.

The following SDAC internal listings will be generated to facilitate the write-up of the SDAC final report. The listings will also be provided to the manuscript writing team. SDAC public IDs will be used and no identifying dates will be provided.

a. Per infant listings of baseline events, AEs and SADRs with site and team assessment of drug attribution.
b. Per infant listing of ARVs from TXW0276 and PE0421.

4.7 Safety Analysis for Dose Finding and Possible Early Study Discontinuation

Purpose:

To list the endpoints and summary tables of safety analysis for dose finding and possible early study discontinuation. Reports will be generated at full accrual to cohort 1 and at interim and full accrual to cohort 2.

Analysis Program Validation:
Code review required. Primary analysis will require double coding.

Data:
Infant Safety Data are adverse clinical and laboratory events reported in Hematology and Liver Chemistries ((LBW0093), Signs/Symptoms (PE6831), Diagnosis (PE6852) and Death (PE1414) CRFs. (The following variables in the SDAC SAS datasets will be used: EVENTDSC, EVNGRDE, FORMNM and FORMTYP in EVENTS table; TRACKCD and RELATSP in TRAC table; and RAL1ST, RAL1RS, RAL2ST, RAL2RS in TXW0276 CRF).

Analysis:
Infants who have been excluded from the PK analyses, due to evidence of problematic exposure to the study medication, will be excluded from evaluation of the safety guidelines. AEs and SADRs will exclude events classified by the team as "baseline" or "ongoing baseline" events.

a) Safety endpoints for Cohorts 1 and 2 in dose finding and possible early study discontinuation
   - Safety endpoints
     -based on data through 6 weeks (i.e. through 49 days) of life:
     i. Life threatening event or death judged to be a SADR or Grade 4 event that is judged to be probably or definitely attributable to the study medication
     ii. Treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related

   Notes: During the regular monitoring, the team will assess whether an AE is life threatening and the assessment will be entered in the TRAC table. Treatment discontinuation due to an AE will be on the TXW0276 CRF.

b) Summary table for the interim and cohort full accrual safety reports (analysis for dose finding and possible early study discontinuation).
   Note: Only the overall summary will be provided since we are expecting very few infants meeting the safety endpoint.

   Table: Summary table showing number (%) of the proportion of infants who meet the safety endpoints for dose finding and possible early study discontinuation.

Table 7: Summary of Infants Meeting the Safety Endpoints for Dose Finding and Possible Early Study Discontinuation

Endpoint	Number and Proportion
Life threatening adverse event or death judged to be a SADR or Grade 4 event that is judged to be probably or definitely attributable to the study medication	
Treatment discontinuation due to non-life threatening Grade 3 or 4 severity SADR, judged to be at least possibly treatment related	
Meeting any of the two safety guideline endpoints	

4.8 Infant Infection Testing

Purpose:
To describe the infant HIV infection status.

Analysis Program Validation:
Not required.

Data:
INFECT2 table holds the infection status of the participants while on study follow-up. Site assessment of infant infection status will be in INFECT2. HIV DNA test results will be in DNALDMS, and HIV RNA results will be in L_RNAFIN and F3109.

Analysis:

Table: Tabulation of infection status of the infants from the INFECT2 table.

4.9 Genotype Analysis

Purpose:
To list the tables for investigating the relationship between neonatal RAL elimination (as reflected in CL/F) and UGT1A-1 genotype, and the relationship between UGT1A-1and SLCO1B3 with hyperbilirubinemia.

Analysis Program Validation:
Code review required.

Data:
HUMGENO table and LBW0093 CRF (TBILCV, BILPHOTO, BILTRANS, BILOTH and BILOTHSP).

Analysis:

a) Response variables for genotype analysis:
   - UGT1A-1 genotype (presence or absence of *28/*28 genetic variant):
     Wild-type: (TA)6(TA)6; mutation: (TA)5(TA)6, (TA)6(TA)7 and (TA)7(TA)7
   - SLCO1B3 (rs2117032-C/T) genotype:
     C/C, C/T and T/T
   - Hyperbilirubinemia defined as total bilirubin exceeding 16.0 mg/dL or infant requiring exchange transfusion for hyperbilirubinemia

b) Output tables:

Table: Summary descriptive statistics (N, geometric mean, median, 25th and 75th percentiles, min, and max) on CL/F will be generated for the subgroups of participants depending on whether they exhibit the UGT1A-1 polymorphism.

Table 8: Summary of Infant RAL CL/F between UGT1A1 Genotype Groups for Cohort 1 (mock-up table)

		UGT1A1 Genotypes							
		Wild-type	**Mutation**				**Overall**	**p-value[a] for all genotypes**	**p-value[b] for wild-type vs. mutation**
		(TA)6(TA)6	**(TA)5(TA)6**	**(TA)6(TA)7**	**(TA)7(TA)7**	**Overall**			
CL/F of RAL-naïve Infants	N								
	mean								
	median								
	…								
CL/F of RAL-Exposed Infants	N								
	mean								
	median								
	…								
CL/F of All Infants	N								
	mean								
	median								
	…								

a Comparison of median among different genotypes will use Kruskal–Wallis test for CL/F of all infants only. The formal comparison will be done only if we have enough infants in the listed genotype groups.

b Comparison of median between wild-type vs. mutation will use Wilcoxon Rank Sum Test for CL/F of all infants only. The formal comparison will be done only if we have enough infants in the listed genotype groups.

Table 9: Summary of Infant RAL CL/F between UGT1A1 Genotype Groups for Cohort 2 (mock-up table)

		UGT1A1 Genotypes					
		Wild-type	**Mutation**				**Overall**
		(TA)6(TA)6	**(TA)5(TA)6**	**(TA)6(TA)7**	**(TA)7(TA)7**	**Overall**	
CL/F from the 1st intensive PK analysis	N						
	mean						
	median						
	…						
CL/F from the 2nd intensive PK analysis	N						
	mean						
	median						
	…						

Note: This table is for Cohort 2 RAL-naïve group only and should we have data on Cohort 2 RAL-exposed group, additional columns for: (i) RAL-exposed group, and (ii) Overall Cohort 2, will be added. Formal comparisons for all Cohort 2 infants will be done by then.

Table: Association between UGT1A-1 genotypes and hyperbilirubinemia (yes/no) with Fisher's Exact Test.

Table 10: Summary of Cohort 1 Infant Hyperbilirubinemia between UGT1A1 Genotype Groups (mock-up table)

Characteristic		Wild-type	Mutation				Overall (N=0)	P-value* for all genotype groups	P-value* for Wild-type vs. Mutation
		(TA)6(TA)6	(TA)5(TA)6	(TA)6(TA)7	(TA)7(TA)7	Overall			
Hyperbilirubinemia	Yes	0	0	0	0	0	0	0.000	0.000
	No	0	0	0	0	0	0		

*Fisher's Exact Test. The power of test will depend upon the distributions of the variables to be analyzed, but will be extremely limited due to the small sample size.
Note: Similar table will be created for Cohort 2 infants.

Table: Association between SLCO1B3 genotypes and hyperbilirubinemia (yes/no) with Fisher's Exact Test.

Table 11: Summary of Cohort 1 Infant Hyperbilirubinemia among SLCO1B3 Genotype Groups (mock-up table)

Characteristic		C/C (N=0)	C/T (N=0)	T/T (N=0)	Total (N=0)	P-Value*
Hyperbilirubinemia	Yes	0	0	0	0	0.000
	No	0	0	0	0	

*Fisher's Exact Test. The power of test will depend upon the distributions of the variables to be analyzed, but will be extremely limited due to the small sample size.
Note: Similar table will be created for Cohort 2 infants.