Combined Clinical and Cross-Discipline Team Leader Review

Date	November 1, 2017
From	Amol Purandare MD Medical Officer
Through	Prabha Viswanathan MD Cross-Disciplinary Team Leader
Subject	Clinical and Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205786/S-006, 22145/S-037, 203045/S-014
Applicant	Merck
Date of Submission	May 25, 2017
PDUFA Goal Date	November 25, 2017
Proprietary Name / Established (USAN) names	Isentress (raltegravir)
Dosage forms / Strength	Oral suspension 100 mg/10 mL
Proposed Indication(s)	ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients
Recommended:	Approval

1. Introduction

This review presents the main findings for Merck's supplemental NDA for Isentress (raltegravir) from IMPAACT Protocol 1110, presented by Merck as Study P080, entitled *A Phase 1 Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in Human Immunodeficiency Virus-1 (HIV-1)-Exposed Neonates at High Risk of Acquiring HIV-1 Infection.* This review highlights the pharmacokinetics, safety and overall risk/benefit assessment that support extending the approval of raltegravir to include full term neonates (birth to < 28 days of age).

2. Background

Raltegravir is an HIV integrase strand transfer inhibitor class antiviral available for oral use. It inhibits catalytic activity of HIV integrase, a necessary enzyme of HIV-1 replication. By this mechanism, raltegravir prevents insertion of the HIV genome into the host genome and stops production of new infectious viral particles.

Raltegravir was approved in the United States in October 2007 for treatment of HIV-1 infection in treatment naïve and experienced adults. The first pediatric approval was issued in December 2011 for children 2 years of age and older, followed by the approval for pediatric patients ≥ 4 weeks to 2 years of age in December 2013. Raltegravir is currently available in the United States marketed as brand name Isentress. Current formulations include tablets in 600mg and 400mg base, chewable tablets in 25mg and 100mg base, and powder in 100mg base per packet. The applicant seeks to extend the indication down to patients who are neonates ages 0-28 days.

The Sponsor proposes the following dose and dosing schedule for neonates, in which the total daily dose of raltegravir is increased to reflect maturation of the UGT1A1-mediated glucuronidation pathway. If the mother has taken raltegravir 2-24 hours before delivery, the neonate's first dose should be given between 24-48 hours after birth.

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing †	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily
*The dosing recommendations are based on approximately 1.5 mg/kg/dose. †The dosing recommendations are based on approximately 3 mg/kg/dose.	

This application was submitted in response to a Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) issued to NDA 203045 on March 16, 2012:

1881-1 Deferred pediatric study under PREA to evaluate the safety and pharmacokinetics of raltegravir in HIV-exposed neonates (born to HIV-infected mothers). This multiple-dose pharmacokinetic and safety study will evaluate raltegravir in addition to the standard of care in HIV-exposed neonates from ages 0 to 4-6 weeks. HIV-exposed neonates will have safety assessments, on or off treatment (as appropriate), for a minimum of 24 weeks after start of raltegravir therapy.

The Sponsor also cross-references data in the current submission to NDA 203045 (raltegravir chewable tablets) and NDA 22145 (raltegravir tablets) since all formulations share the same prescribing information.

3. CMC/Device

There are no significant CMC or device findings. Manufacture and packaging of raltegravir powder has not changed since the original NDA review. Dose packaging continues to be 100mg per sachet. Facilities reviewed for drug product and assembly were found to have no issues in the past.

There is a packaging and reconstitution change with the product. Prior manufactured product cartons contained a single 5 mL syringe for reconstitution and dosing. New packaging will include 3 syringes in sizes of 1mL, 3mL, and 10mL for the reconstitution and dosing. Currently, raltegravir powder is approved for 5ml resuspension; the change with syringes adjusts

reconstitution to be done in 10mL of water. This results in greater volume of suspension, which is necessary to allow more precise dosing of smaller children. There are no changes in the provided mixing cups. Syringe and mixing cups are food grade safe and environmentally acceptable. Further detail is provided in the CMC review by Dr. Allan Fenselau. CDRH also reviewed the product given changes to the co-packaged syringes, and details can be found in the review by Janice Ferguson.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies for raltegravir have been reviewed in prior submissions. No new nonclinical pharmacology/toxicology studies were submitted in the current sNDA.

5. Clinical Pharmacology/Biopharmaceutics

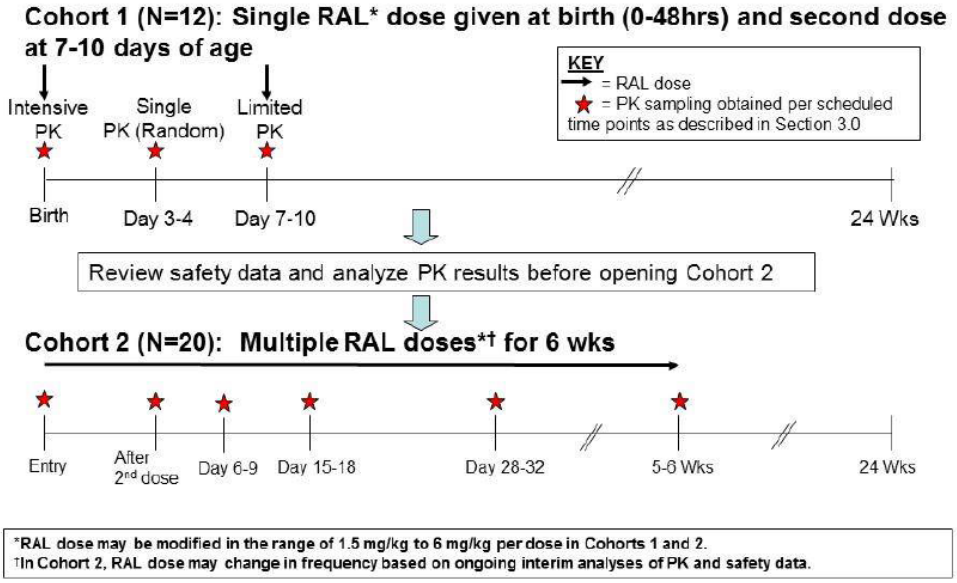
Analyses of the pharmacokinetic (PK) data are an essential part of this supplemental NDA because efficacy can be extrapolated from adults for conditions such as HIV, in which the disease course and response to therapeutic agents (raltegravir in this case) are similar in adult and pediatric subjects. Hence, the primary objective of study P1110 was to demonstrate that the proposed neonatal dosing schedule produces raltegravir PK exposures that match the adult exposures deemed safe and effective. The PK/PD or exposure-response analyses conducted during the original adult Phase 2 and 3 trials did not identify specific pharmacokinetic parameters that correlated with efficacy outcomes. The influence of raltegravir concentrations on treatment outcome was most evident for subjects with very limited or no active optimized background therapy (OBT). Therefore, the goal of the pediatric dose selection was to target the adult exposure (AUC12) with 400 mg BID, which is known to be an effective dose. Prior approvals for pediatric use of raltegravir relied on PK and safety data from study P1066, which demonstrated that the arithmetic mean raltegravir AUC_{12} fell within the target range of 14 to 25 μM*hr and the mean C_{12} values exceeded the target of >33 ng/mL.

Data from P1066 were used to inform dose selection for P1110, along with data from IMPAACT P1097, which evaluated mother-neonate pairs enrolled prior to delivery or within 48 hours after birth. The results indicated raltegravir clearance was substantially lower in the first days of life/ this observation helped construct the initial dosing regimen for IMPAACT P1110.

5.1 IMPAACT P1110 Dosing Regimen

Two cohorts of neonates were evaluated in IMPAACT P1110 (Figure 1). The primary purpose of Cohort I was to generate PK data that could be combined with historical pediatric PK data from older raltegravir-treated infants and children in a population PK model. Using modeling and simulation, a daily raltegravir dosing regimen could be constructed to be evaluated in Cohort II. The purpose of Cohort II was to evaluate the PK and safety of raltegravir administered during the first 6 weeks of life, which is the standard duration of infant prophylaxis for infants at high-risk of HIV-1 infection. In addition to the assessment of safety through 6 weeks of age, the study also assessed safety through 24 weeks (approximately 6 months of age).

Figure 1: P1110 Study Schema



Source: P080 Clinical Study Report, Figure 9-2

In Cohort I, the first dose was given within 48 hours of birth and the second dose between 7 and 10 days of life. The first dose provided PK data when infant glucuronidation is at its lowest point, and the second dose between 7 to 10 days of life provided data about metabolic changes. In Cohort II, raltegravir was administered daily for 6 weeks with changes at Day 7 and 28 in dose (in the range of 1.5– 6 mg/kg/dose) and/or frequency (once or twice daily) to reflect maturation of the metabolic pathway.

PK sampling was done on Days 3-4, Day 14, Day 28 and 6 weeks of age. The PK targets differed for Cohort I and Cohort II. The PK targets for Cohort I were based on safety targets established on mean exposure observed from the adult raltegravir QTc study; the raltegravir exposure targets were not to exceed AUC_{12} of 28 mg*hr/L and C_{max} of 8724 ng/mL. The Cohort II dosing regimen was developed from PK data from Cohort I along with data from prior studies P1066 and P1097. The PK targets for once-daily dosing were GM AUC_{24} between 12 and 40 mg*hr/L and C_{24} >33 ng/mL; similarly, PK targets for twice- daily dosing were GM AUC_{12} between 6 and 20 mg*hr/L and C_{12} >33 ng/mL.

5.2 Pharmacokinetic Results

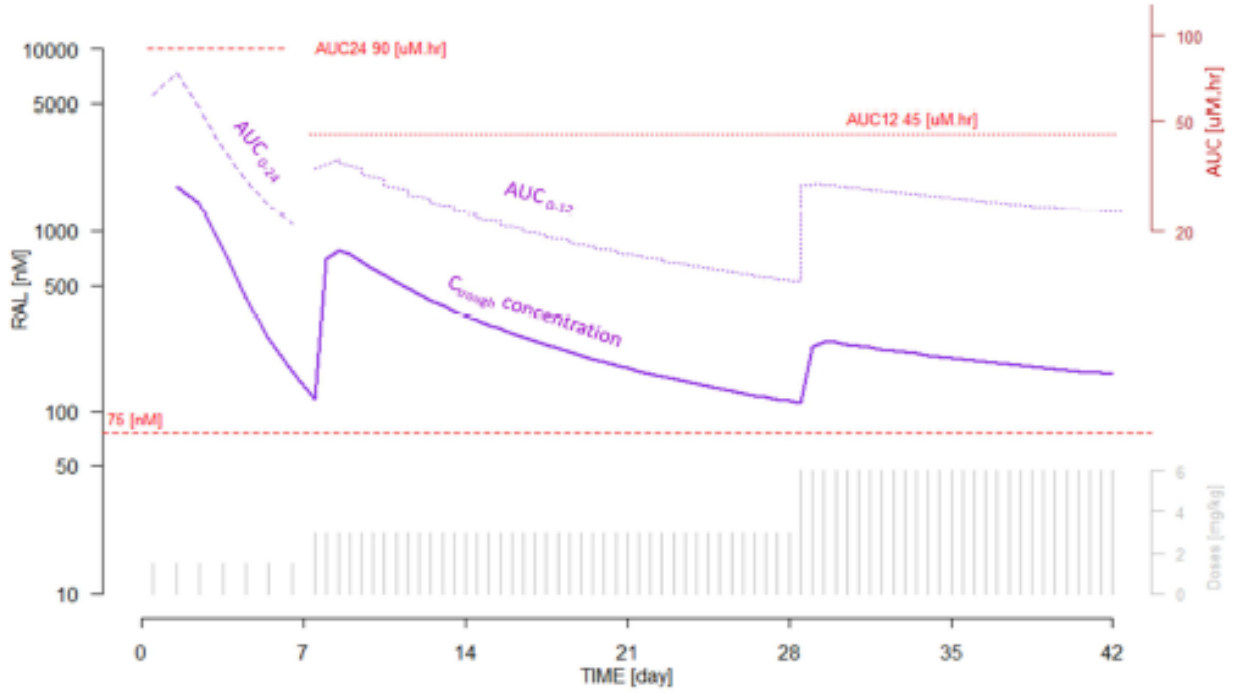
5.2.1 Cohort 1

Fifteen of the 16 infants were PK evaluable (9 raltegravir unexposed, 6 raltegravir exposed). An initial dose of 3mg/kg administered to 6 raltegravir-unexposed neonates resulted in geometric means (GMs) of AUC_{12} and C_{max} of 29.48 mg*hr/L and 3360.89 ng/mL, respectively. None of the individuals exceeded the C_{max} target, but the AUC target was surpassed by 3 of the 6 neonates. Due to this, the initial dose was lowered to 2 mg/kg, which resulted in C_{max} below the maximal threshold in 3 PK-evaluable neonates, but AUC_{12} values of 17, 29, and 44 mg*hr/L. In Cohort I there were also 6 raltegravir-exposed, PK evaluable neonates, with the same C_{max} and AUC_{12} target goals. The subjects were given an initial dose of 1.5mg/kg dose (lower due to in utero exposure) and had subsequent GM AUC_{12} and C_{max} of 20.3 mg*hr/L and 2188.8 ng/mL,

respectively. None of the individuals exceeded the C_{max} target, yet the AUC_{12} target was exceeded by 4 out of the 6 neonates.

A population PK model was developed using the 6 subjects who received 2 single doses of 3 mg/kg within 48 hours of age and 7-10 days of age along with historical pediatric data to support a 6-week dosing recommendation for Cohort II. Simulations included 10 candidate dosing regimens designed to attain the PK targets (C_{trough} > 33.3 ng/mL, C_{max} <8720 ng/mL, AUC_{24} <40 hr*mg/L, AUC_{12} <20 hr*mg/L). Ultimately, the dosing regimen recommended for raltegravir-unexposed neonates in Cohort II consisted of 1.5 mg/kg QD from birth through day 7 of age (week 1), followed by 3 mg/kg BID during days 8 through 28 (weeks 2 to 4), and 6 mg/kg BID during days 29 through 42 (weeks 5 and 6). This regimen was predicted to meet all PK endpoints, as illustrated in Figure 2.

Figure 2 Simulated Daily AUC and Ctrough Values for the Recommended 6-week Dosing Regimen



Source: P080 Clinical Study Report, Figure 11-4

The Clinical Pharmacology team reviewed the model and found it to be acceptable. Please see Dr. Zvada's clinical pharmacology review for additional details.

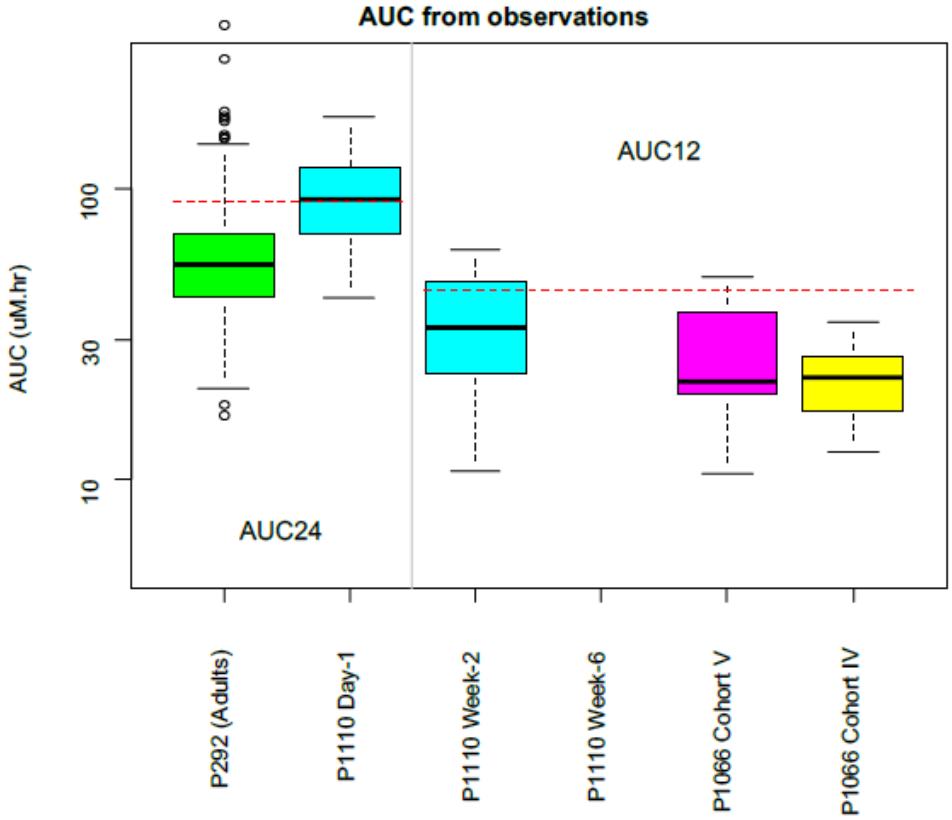
5.2.2 Cohort 2

There were 25 PK-evaluable neonates in Cohort II. The GM after the first dose of 1.5 mg/kg once daily was 38.20 hr*mg/L for AUC_{24} and 947.9 ng/mL for C_{24}. After a dose of 3 mg/kg twice daily at Day 15 to 18 of age, GM for AUC_{12} was 14.30 hr*mg/L and GM of C_{last} was 557.99 ng/mL.

The median trough level went down after the first dose on Day1 to 69.3 ng/mL after one week of 1.5 mg/kg once daily dosing. This is reflective of UGT-1A1 maturation, resulting in increased raltegravir clearance, and thereby necessitating a dose increase to 3 mg/kg twice daily after one week of life. The median trough levels again decreased from 326 ng/mL in Week 2 to 82 ng/mL in Week 4, again reflecting further maturation of the UGT-1A1 enzyme complex. Following the second dose increase at 4 weeks of age (from 3 mg/kg to 6 mg/kg twice daily), the median trough level obtained at Weeks 5 to 6 was 104 ng/mL.

Figures 3 and 4 provide a graphical representation of AUC and C_{trough} for subjects in P1110 compared to a pediatric population of children older than 4 weeks from Study P1066 and an adult population from Study 292 (AUC only). Observed data were insufficient to determine AUC_{12} levels for neonates in the 5-6 week age group.

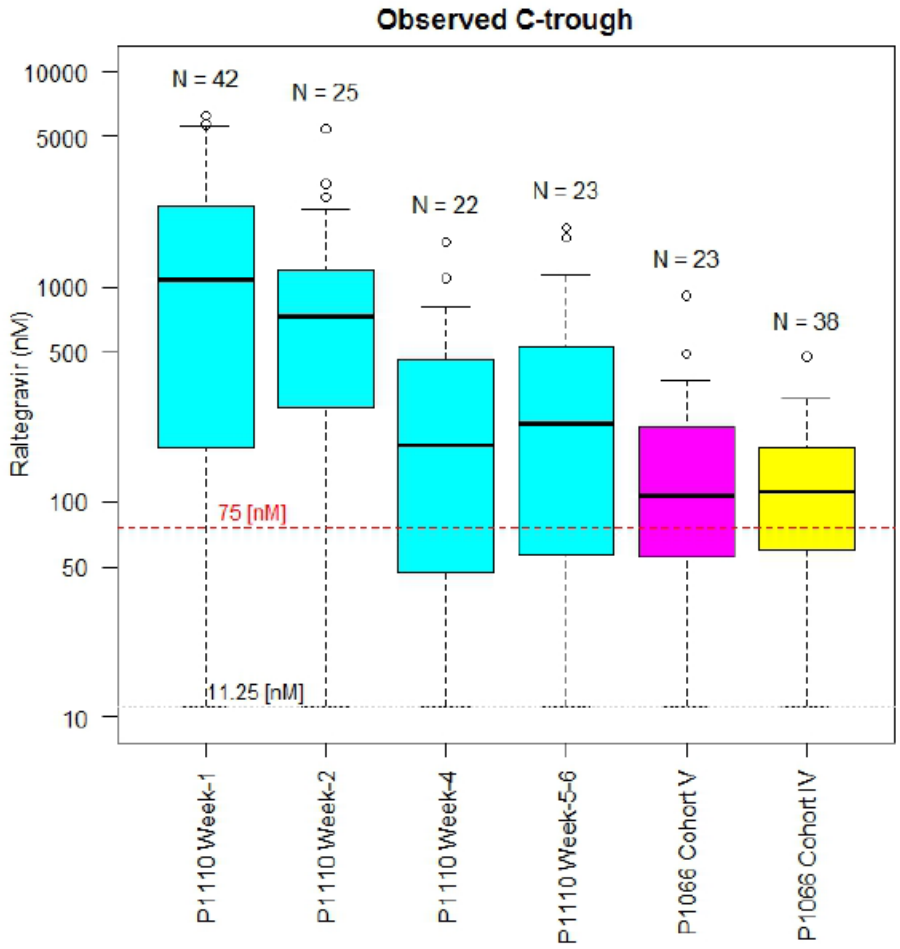
Figure 3 Boxplots of Observed Raltegravir AUC



Source: Modeling and Simulation Report, Figure 4-13

*Medical Officer Comment: The pre-specified target raltegravir exposures were AUC_{24} between 12 and 40 mg*hr/L and AUC_{12} between 6 and 20 mg*hr/L. The first dose resulted in a mean exposure at the top of the target range, with 5/10 raltegravir-unexposed neonates exceeding 90mg*hr/L. The mean AUC_{12} at Week 2 (following the dose increase) was within the target range but 3/9 subjects exceeded 45 mg*hr/L.*

Figure 4 Boxplots of Observed Raltegravir Trough Samples



Source: Modeling and Simulation Report, Figure 4-12

Medical Officer Comment: At each timepoint assessed, the median C_{trough} met the pre-specified target of > 33.3 ng/mL. This finding validates that the proposed dosing schedule, which includes dose increases at Week 1 and Week 4, appropriately accounts for UGT-1A1 maturation to maintain raltegravir concentrations at a therapeutic level.

In order to determine the risk of overexposure for smaller patients and underexposure for larger patients, the Sponsor provided a summary of predicted PK profiles of raltegravir-unexposed neonates at the extreme ends of the proposed weight bands (Table 1). Neonates at the lower end of each weight band are predicted to exceed the AUC_{24} limit of 40 mg*hr/L after the second dose of raltegravir, but this is expected to last for only 1 to 2 days. The highest raltegravir concentration predicted is 6580 ng/mL for a 2 kg neonate, which is well below the safety threshold of 8720 ng/mL. Neonates with body weights at the high end of each weight band were predicted to maintain a C_{trough} well above the target of 33 ng/mL.

Table 1 Raltegravir Exposures for Raltegravir-Unexposed Neonates at the Extremes of Weight Bands

		Dose regimen			Concentration		AUC 0-24			AUC 0-12		
Weight band	Body Weight (kg)	QD Week 1 (mg)	BID Week 2-4 (mg)	BID Week 5-6 (mg)	Min. (nM)	Max. (nM)	Max. (μM.hr)	Max. fold	Days >90	Max. (μM.hr)	Max. fold	Days >45
2 to < 3 (kg)	2	4	8	20	177	14800	115	1.3	2	54.8	1.2	13.5
	3	4	8	20	138	10600	82.1	0.9	0	40.2	0.9	0
3 to < 4 (kg)	3	5	10	25	173	13200	103	1.1	1	50.2	1.1	7.5
	4	5	10	25	145	10400	80.8	0.9	0	40.2	0.9	0
4 to <5 (kg)	4	7	15	30	217	12500	113	1.3	1	60.3	1.3	8
	5	7	15	30	189	10300	93.8	1	1	50.8	1.1	2.5

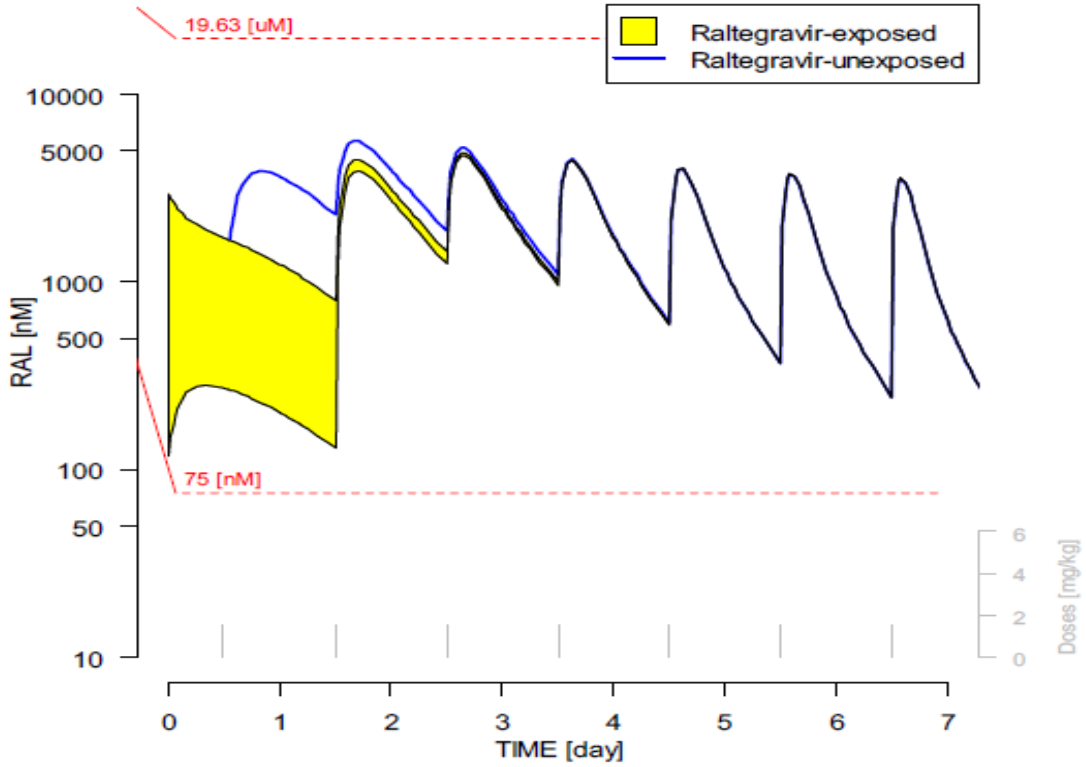
Source: Modeling and Simulation Report, Table 4-12

5.3 Dosing Considerations for Raltegravir-Exposed Neonates

IMPAACT P1110 enrolled only a small number of raltegravir-exposed infants (n=6), and all subjects were in Cohort 1. Hence, there are no observed PK data from raltegravir-exposed neonates who received daily dosing using the proposed dosing schedule. To fill this data gap, simulations were performed to determine how the time span between the last maternal dose and birth affects raltegravir exposures in the neonate. If the first dose is administered to a raltegravir-exposed neonate at 36 hours of life, raltegravir C_{trough} concentration is predicted to range from 62.2 ng/mL (assuming a 24 hour timespan between last maternal dose and birth) to 667 ng/mL (assuming a 2 hour timespan between last maternal dose and birth). These trough concentrations exceed the target C_{trough} of 33.3 ng/mL. In either case, the AUC_{24} is predicted to stay within the upper limit of 40 μg.hr/mL.

The Sponsor also conducted an analysis to predict how raltegravir exposures compare between raltegravir-exposed and raltegravir-unexposed infants if the first dose is given 36 hours after birth to raltegravir-exposed neonates, and 12 hours after birth to raltegravir-unexposed neonates. As shown in Figure 5, the exposure curves are nearly identical by Day 2 and overlap by Day 3.

Figure 5 Time-Course Raltegravir Exposures of Raltegravir-Exposed Compared to Raltegravir-Unexposed Neonates



Birth a TIME=0 (day). First dose administration 36 hours after birth to raltegravir-exposed (yellow area) and 12 hours after birth to raltegravir-unexposed (blue solid line) neonates. The yellow area represents the range of simulated concentrations of raltegravir-exposed neonates immediately after birth and after subsequent dose administrations, which depends on the time of administration of the last dose to the mother (between 2 to 24 hours before delivery).

Source: Modeling and Simulation Report, Figure 4-20

Medical Officer Comment: This analysis supports the Sponsor's proposal to delay raltegravir dosing 24-48 hours after birth to raltegravir-exposed neonates. This delay will help mitigate the risk of adverse drug reactions caused by high exposures, and is not expected to impact efficacy given that the C_{trough} is predicted to remain well above 33 ng/mL (75nM).

5.4 Conclusions

The observed and modeled PK data support the proposed dosing regimen for the treatment of HIV in neonates. At the studied doses, subjects were able to achieve and maintain raltegravir concentrations above the target concentration identified for efficacy (33.3 ng/mL). Although mean AUC_{24} is at the highest end of the target range after the first dose, and exceeded by some infants, these levels are not expected to be sustained for more than 1-2 days as the UGT enzyme matures. There is extensive clinical experience with raltegravir in both adults and children, and no exposure-safety concerns have emerged to date. Therefore, these transiently elevated exposures are not expected to be clinically significant.

Please refer to Clinical Pharmacology review by Simbarashe Zveda, Ph.D. for additional details.

6. Clinical Virology

No virology data are available because P1110 evaluated HIV-exposed, uninfected neonates. All subjects remained HIV-negative at Week 24.

7. Clinical/Statistical- Efficacy

Overview

Study P1110 provides pivotal PK and safety data to support use of raltegravir in neonates. In contrast to prior trials evaluating the safety and efficacy of raltegravir in HIV-1 infected subjects, P1110 evaluated HIV-1 exposed neonates at high risk for mother to child transmission (MTCT). The Sponsor contends, and DAVP agrees, that these data can be used to support dosing recommendations for HIV-1 infected neonates if PK data show that the studied neonatal dosing regimen results in AUC and C_{trough} in the target range from approved adult doses. As described in Section 5, the raltegravir exposure target were met.

7.1 Summary of Trial Design

P1110 was to enroll approximately 50 mother-infant pairs, with a minimum of 32 PK-evaluable HIV-1 exposed neonates. In Cohort I, a minimum of 12 neonates were to be enrolled, with the goal of characterizing UGT maturation and to help inform raltegravir dosing for Cohort II. Cohort II planned a minimum of 20 neonates to receive raltegravir for 6 weeks in addition to standard of care PMTCT prophylactic antiretroviral therapy.

Key inclusion criteria required enrolled subjects to be HIV-1-exposed neonates of at least 37 weeks gestation and 2 kg of weight and aged ≤48 hours. Infants might have received up to 48 hours of standard of care antiretroviral therapy prophylaxis before enrollment. Mothers were either known to have been HIV-1 infected prior to labor or identified as HIV-1 infected at the time of labor or in the immediate postpartum period. The parent or legal guardian needed to be able and willing to sign informed consent. Mother-infant pairs were enrolled and the infant must have received the first raltegravir dose within 48 hours of birth. All subjects had to be able to take oral medications. All neonates were to have no known severe congenital malformation or other medical conditions not compatible with life or that would have interfered with study participation.

Subjects in Cohort I had a dosing regimen of an initial single dose of 1.5 mg/kg, 2 mg/kg, or 3 mg/kg within 48 hours of birth and a second 3 mg/kg single dose at 7-10 days of age. Cohort II had a dosing regimen of 1.5 mg/kg once daily for first week of life, 3 mg/kg BID for days 8 to 28 of age, and 6 mg/kg twice daily for days 29 of age and beyond. All subjects had follow-up through Week 24. Cohort I subjects were evaluated at baseline, on dosing days, and at age 2 weeks, 6 weeks, and 24 weeks. Cohort II subjects were evaluated at baseline, after the second dose, and at age 6-9 days, 15-18 days, 28-32 days, 5-6 weeks, 8-10 weeks, and 24 weeks.

7.2 Subject Disposition

A total of 42 neonates were enrolled; 16 in Cohort 1 and 26 in Cohort 2. Subject disposition is summarized in Table 2. There were 3 early treatment discontinuations in Cohort II. One was due to an adverse event of Grade 3 weight loss, not deemed related to study drug. The other 2 were

from withdrawal of consent. Of the 4 subjects listed as Early Follow up Discontinuation, 2 subjects were those that withdrew consent early. There were an additional 2 subjects who completed treatment, yet discontinued prior to follow up due to guardian consent withdrawal.

Table 2 Study Disposition of All Treated Neonates

Disposition	*Cohort I (RAL unexposed) N= 10 (%)*	*Cohort I (RAL exposed) N = 6 (%)*	*Cohort 1 Total N = 16 (%)*	*Cohort II (RAL unexposed) N = 26*
Treated	10 (100.0)	6 (100.0)	16 (100.0)	26 (100.0)
Completed Treatment	10 (100.0)	6 (100.0)	16 (100.0)	23 (88.5)
Early Treatment Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)
Non-protocol defined high grade AE	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Guardian consent withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)
Completed Follow up	10 (100.0)	6 (100.0)	16 (100.0)	22 (84.6)
Early Follow up Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)

Source: Adapted from P080 Clinical Study Report, Table 10-3, using F1601 and PE4005 datasets

Medical Officer Comment: *There are no MO concerns with subject disposition. Adequate explanations for disposition were provided.*

7.3 Demographics

Forty-two children at high risk for HIV transmission were enrolled from 13 study centers located in the United States, Brazil, and South Africa. The centers included 9 from the United States, 3 from Brazil, and 1 from South Africa, which fits with the given demographic distribution listed in Table 2.

Mothers in Cohort I had a median age of 24.5 years; 69% of mothers were Black and 31% were Hispanic. In Cohort II, the median maternal age was 27 years; 69% were Black and 73% were Hispanic. Maternal characteristics which placed infants at high risk for transmission included: HIV RNA > 1000 copies/ml within 4 weeks of delivery (23/42, 55%); no maternal ARVs during current pregnancy (4/42, 10%); on ARVs < 4 weeks prior to delivery (16/42, 38%); resistance to at least of ARV class (8/42 19%). Maternal antiretroviral therapies most frequently used at delivery in both Cohort I and Cohort II were protease inhibitor (PI) based regimens (31% and 39%, respectively), followed by integrase inhibitor ± nucleoside reverse transcriptase inhibitor (NRTI) regimens in Cohort I (19%) and non-nucleoside reverse transcriptase inhibitor (NNRTI) +/- NRTI regimens in Cohort II (23%).

Table 3 depicts demographic characteristics of neonates in the study population, and Table 4 summarizes baseline birth characteristics of the evaluated neonates.

Table 3 Demographic Characteristics

Neonatal Baseline Characteristics by Cohort - All Treated Neonates

	Cohort I RAL unexposed (N=10) n (%)	Cohort I RAL exposed (N=6) n (%)	Total (N=16) n (%)	Cohort II RAL unexposed (N=26) n (%)
Gender				
Male	4 (40)	4 (66.7)	8 (50)	14 (53.8)
Female	6 (60)	2 (33.3)	8 (50)	12 (46.2)
Race				
Black or African American	9 (90)	2 (33.3)	11 (68.8)	18 (69.2)
White	0 (0)	2 (33.3)	2 (12.5)	3 (11.5)
Multi-racial	1 (10)	0 (0)	1 (6.3)	0 (0)
Other	0 (0)	1 (16.7)	1 (6.3)	5 (19.2)
Unknown	0 (0)	1 (16.7)	1 (6.3)	0 (0)
Ethnicity				
Hispanic or Latino	2 (20)	3 (50)	5 (31.3)	19 (73.1)
Not Hispanic or Latino	7 (70)	2 (33.3)	9 (56.3)	7 (26.9)
More than one ethnicity	1 (10)	0 (0)	1 (6.3)	0 (0)
Unknown	0 (0)	1 (16.7)	1 (6.3)	0 (0)
Birth Outcome				
Live birth	10 (100)	6 (100)	16 (100)	26 (100)
Mode of Delivery				
Spontaneous vaginal	3 (30)	0 (0)	3 (18.8)	5 (19.2)
Cesarean section	7 (70)	6 (100)	13 (81.3)	21 (80.8)

Abbreviations: N = Number of neonates in each cohort, n (%) = Number (percent) of neonates in each subcategory, RAL = raltegravir

Source: P080 Clinical Study Report, Table 10-5

Medical Officer Comment: Although not all study participants are from the United States, the racial and ethnic make-up are well representative of demographics in the US. The high percentage of Cesarean deliveries is likely due to ongoing HIV viremia among mothers, an indicator of high risk of vertical transmission for their infants.

Table 4 Baseline Birth Characteristics

		Cohort I			Cohort II
		RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)	RAL unexposed (N=26)
Gestational age at birth (weeks)	n	10	6	16	26
	median	39	38	38.5	38
	q1,q3	38,39	37,39	38,39	37,39
	min,max	38,40	37,40	37,40	37,40
	mean (std dev)	38.7 (0.7)	38.2 (1.2)	38.5 (0.9)	38.2 (1.1)
Birth weight (gram)	n	10	6	16	26
	median	3020	2947.5	3017	2930
	q1,q3	2845,3380	2530,3285	2822.5,3332.5	2690,3070
	min,max	2385,4200	2320,3385	2320,4200	2390,3745
	mean (std dev)	3136 (520.6)	2902.5 (417.5)	3048.4 (484.1)	2951.4 (349.2)
Birth length (cm)	n	10	6	16	25*
	median	48.5	48.5	48.5	49
	q1,q3	47,51	47,50	47,51	48,50
	min,max	47,53	47,52	47,53	46,53
	mean (std dev)	49.3 (2.3)	48.8 (2)	49.1 (2.1)	49.2 (1.8)
APGAR score at 1 minute of life	n	10	6	16	26
	median	8	8.5	8	9
	q1,q3	8,9	8,9	8,9	8,9
	min,max	8,9	8,9	8,9	6,10
	mean (std dev)	8.4 (0.5)	8.5 (0.5)	8.4 (0.5)	8.5 (0.8)

Source: P080 Clinical Study Report, Table 10-6

Medical Officer Comment: HIV infection in pregnant women (treated and untreated) has been associated with a variety of adverse pregnancy outcomes, including preterm delivery, intrauterine growth retardation, and low birth weight. This cohort of full-term neonates exhibits normal birth weight and length and good health status at birth, as assessed by the APGAR score.

All neonates received standard of care (per local practice) antiretroviral agents for PMTCT in addition to raltegravir study treatment. The most frequently used regimens consisted of NNRTI +/- NRTI (56.3% in Cohort I and 96.2% in Cohort II), most frequently nevirapine (NVP) plus zidovudine (ZDV). There were only five subjects who didn't receive ZDV (1 in Cohort I, 4 in Cohort II), all of whom received NVP alone.

7.4 Additional Efficacy Issues/Analysis

All 42 subjects received appropriate testing for evidence of HIV-1 infection within 48 hours of birth, and at 6 and 24 weeks of life. If subjects were found to have HIV-1 infection during the study, resistance testing towards raltegravir and other antiretroviral medications would be performed after confirmation of vertical transmission. There were no subjects that tested positive during study or follow up time period.

7.5 Efficacy Conclusions

As described in Section 5, the raltegravir exposures in study P1110 are in the target range of safe and effective exposures established for adults treated for HIV-1 infection. Although the study participants in P1110 were not HIV-1 infected, there are no compelling data to suggest that the exposures needed for prevention would be higher than those needed for treatment. In fact, although the optimal doses are not known for infant ARV prophylaxis, the dosage and dosing interval recommended by the Department of Health and Human Services Perinatal Treatment Guidelines for infant prophylaxis include ARV dosing regimens identical to, or lower than, the approved treatment doses. [1] Therefore, the current data support extrapolation of efficacy from adults to full term neonates for treatment of HIV infection. The appropriate dose of raltegravir in pre-term neonates remains unknown.

Efficacy of raltegravir as a PMTCT measure cannot be established with these data because there are no adult data (PK and efficacy) from which to extrapolate. (b) (4)

8. Safety

8.1 Overview and Methods

All safety data reviewed in this submission came from a single trial, IMPAACT P1110. Study IMPAACT 1110 is a Phase 1, multicenter, open label, non-comparative study to evaluate the safety and PK of raltegravir administered to neonates exposed to HIV-1 in utero and at high risk of acquiring HIV-1 infection via vertical transmission. The safety population included all subjects who received at least one dose of study medication (n=42). Safety data were analyzed by the clinical reviewer using JReview 11 and JMP12 software.

The primary safety endpoint was the incidence of all adverse events, including serious adverse events and drug related adverse events. Laboratory abnormalities (e.g. hyperbilirubinemia, hematology, and chemistry) and vital signs, recorded through 6 weeks of life, were also part of primary safety endpoints. Secondary safety endpoints evaluated similar data on adverse events and laboratory abnormalities through 24 weeks of life. Additional focused analyses were based on investigating pharmacokinetics of raltegravir elimination, hyperbilirubinemia, and role of UGT1A1 and SLCO1B3 genotypes. Because the study did not have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences, descriptive statistics are used to describe the observed findings.

8.2 Categorization of Adverse Events

The adverse events (AE) in this study were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0. The AEs were categorized by MedDRA Preferred Term and

[1] Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. [Table 7]. Available at https://aidsinfo.nih.gov/guidelines/html/3/perinatal/187/infant-antiretroviral-prophylaxis. Accessed October 20, 2017.

System Organ Class. Safety data were analyzed by the incidence of clinical and laboratory AEs, serious adverse events (SAEs), relation to study drug, deaths, and treatment related discontinuations of treatment or study. SAEs were defined as AEs which resulted in death, was life-threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged hospitalization was congenital anomaly/defect, or other important medical event. Adverse events that had potential to be study drug-related were graded according to the Division of AIDS (DAIDS) Table of Grading Severity of Adult and Pediatric Adverse Events. In addition to SAEs, investigators also were required to report bilirubin concentrations above 16.0 mg/dL; exchange transfusions for hyperbilirubinemia; all malignancies, seizures, immune reconstitution syndrome events, hepatotoxicity, and Grade 3 or Grade 4 toxicities where relation to treatment cannot be ruled out.

Table 5 Clinical Adverse Events through 6 Weeks of Life

Subjects with AEs	***Cohort I (RAL unexposed) N= 10 (%)***	***Cohort I (RAL exposed) N = 6 (%)***	***Cohort 1 Total N = 16 (%)***	***Cohort II (RAL unexposed) N = 26***
One or more clinical AE	7 (70.0)	4 (66.7)	11 (68.8)	19 (73.1)
No clinical AE	3 (30.0)	2 (33.3)	5 (31.3)	7 (26.9)
One or more clinical SAE	1 (10.0)	1 (16.7)	2 (12.5)	2 (7.7)
One or more Serious drug related clinical AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death due to clinical AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to AE	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
One or more Grade 3/4 clinical AE	1 (10.0)	1 (16.7)	2 (12.5)	2 (7.7)
One or more Grade 3/4 drug related clinical AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from sponsor table 12-2 and events.xpt dataset

Table 6 Laboratory Adverse Events through 6 Weeks of Life

Subjects with AEs	*Cohort I (RAL unexposed) N= 10 (%)*	*Cohort I (RAL exposed) N = 6 (%)*	*Cohort 1 Total N = 16 (%)*	*Cohort II (RAL unexposed) N = 26*
One or more lab AE	9 (90.0)	6 (100.0)	15 (93.8)	21 (80.8)
No lab AE	1 (10.0)	0 (0.0)	1 (6.3)	5 (19.2)
One or more lab SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
One or more Serious drug related lab AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death due to lab AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to labAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
One or more Grade 3/4 lab AE	0 (0.0)	2 (33.3)	3 (18.8)	5 (19.2)
One or more Grade 3/4 drug related lab AE	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)

Source: Adapted from sponsor table 12-4 and events.xpt dataset

MO Comment: *The primary focus of the safety analysis is characterization of treatment emergent adverse events occurring during the 6 week treatment period. Pertinent findings are that no deaths were noted in either the 6 or 24 week time frame. There were no distinct differences between cohorts, suggesting that repeated dosing of raltegravir in Cohort II was as well tolerated as two single doses in Cohort I.*

8.3 Major Safety Results

AEs from the entire 24 week follow up period were also reviewed. Details on major safety results are described below.

8.3.1 Deaths

There were no deaths in this clinical study through the 24 week follow through period.

8.3.2 Nonfatal Serious Adverse Events

Table 6 summarizes all nonfatal serious adverse events (SAEs) reported during the study. There were 9 subjects who experienced a total of 11 serious clinical or laboratory events. Four subjects had SAEs in the first 6 weeks, and the remainder occurred between 6 and 24 weeks (off treatment period). Only one SAE lead to study discontinuation. There is 1 subject in Cohort I with congenital syphilis included in Table 7, not listed in the CSR, yet recorded as an SAE in raw datasets. None of the SAEs were deemed related to raltegravir treatment.

Table 7 Nonfatal Serious Adverse Events through 24 Weeks

SAE by Preferred Term	*Cohort I N= 16 (%)*	*Cohort II N = 26 (%)*	*Cohort I and II N= 42 (%)*
Subjects With SAE	***2 (12.5)***	***7 (26.9)***	***9 (21.4)***
Bronchiolitis	0 (0.0)	2 (7.7)	2 (4.8)
Congenital Syphilis	1 (6.3)	1 (3.8)	2 (4.8)
Anemia, Neonatal	1 (6.3)	0 (0.0)	1 (2.4)
Blood Glucose Decreased	0 (0.0)	1 (3.8)	1 (2.4)
Cellulitis	0 (0.0)	1 (3.8)	1 (2.4)
Craniocerebral injury	0 (0.0)	1 (3.8)	1 (2.4)
Pneumonia	0 (0.0)	1 (3.8)	1 (2.4)
Vomiting	1 (6.3)	0 (0.0)	1 (2.4)
Weight Decreased	0 (0.0)	1 (3.8)	1 (2.4)

Source: Adapted from ar001aes.xpt and events.xpt dataset

Four subjects experienced SAEs during the 6 week treatment period.

1. Subject 8506173 (Cohort 2) had hypoglycemia on day 2 of life which resolved spontaneously.

2. Subject 8505999 (Cohort 1) was noted to have a drop in hemoglobin to 7.6 g/dL on day 22 of life of Grade 4 in severity. The hemoglobin levels gradually rose and recovered by day 32 of life.

   Medical Officer Comment: Given the time frame and being in Cohort I it was reported as anemia neonatal which would clinically fit and is likely not associated with study drug, but possibly related to concurrent antiviral therapy with ZDV which is known to cause decrease in hemoglobin.

3. Subject 7055306 (Cohort 1) experienced 6 episodes of non-bloody, non-bilious emesis on day 3 of life. Symptoms resolved on same day, with no recurrence when the patient was given the second dose on Day 8 of life. The investigator has deemed this not related to study drug.

   Medical Officer Comment: Given the occurrence after the first dose on Day 3 of life with no recurrence, in addition to the fact that spontaneous emesis in the subject's age range can be multifactorial, this MO would consider the AE to be possibly related, though not probably related to study drug.

4. Subject 8506734 (Cohort 2) had a SAE of weight decreased and discontinued study drug. (see section 8.3.5 for narrative). The SAE was deemed not related to study drug, and multifactorial in nature. This subject is described in greater detail in subsequent sections of this review.

Other recorded SAEs of bronchiolitis, cellulitis, pneumonia, craniocerebral injury occurred within the 24 week follow up, with narratives that suggest that they are not related to study drug.

Medical Officer Comment: Overall, there is no clear pattern to the types or timing of SAEs to suggest a relationship to raltegravir, and no specific labeling is warranted.

8.3.3 Significant Adverse Events

There were 14 subjects with Grade 3 and 4 Adverse Events during the first 6 weeks. Of those 14, there were 4 subjects in Cohort I with 6 high grade AEs. In Cohort II there were 12 Grade 3 or 4 AEs documented in 10 subjects.

Table 8 Grade 3 and 4 Adverse Events Through 6 weeks

AEs by Preferred Term	*Cohort I N=16 (%)*	*Cohort II N=26 (%)*
Subjects with AE	***4 (25.0)***	***10 (38.5)***
Neutrophil Count Decreased	1 (6.3)	4 (15.4)
Haemoglobin Decreased	1 (6.3)	2 (7.7)
Blood Pressure Increased	1 (6.3)	1 (3.8)
Anemia, Neonatal	1 (6.3)	0 (0.0)
Blood Bilirubin Increased	0 (0.0)	1 (3.8)
Blood Glucose Decreased	0 (0.0)	1 (3.8)
Blood Potassium Increased	1 (6.3)	0 (0.0)
Hypertension Neonatal	1 (6.3)	0 (0.0)
Congenital Syphilis	1 (6.3)	1 (3.8)
Weight Decreased	0 (0.0)	1 (3.8)

Source: Adapted from PE6863.xpt and TXW0276.xpt dataset

MO Comment: *Narratives were reviewed for all events.*
Cohort 1:Subject 8506030 experienced both Blood Pressure Increased and Hypertension Neonatal; the findings are a continuum of the same process, and not necessarily distinct AEs. Likewise, subject 8505999 was documented as having Anemia neonatal and Haemoglobin decreased, which are not necessarily separate processes. The investigator marked the events as probably drug related, but with the caveat that the events may be related to concomitant medication (ZDV) as well. Given the subject was in raltegravir exposed cohort, it is possible the event is study drug related as in utero exposure may result in cell line suppression, though the role of ZDV as a concomitant ARV causing anemia is possible as well.

Cohort 2: Subject 8506734 experienced 3 high grade AE including Blood bilirubin increased, Haemoglobin decreased, and Weight decreased. The subject was also the only subject to discontinue the study due to adverse events as discussed in following section.

Overall, for all subjects who experienced Grade 3 or 4 AEs, the events do not seem likely to be study drug related, other than in subject 850999 as noted. Neutropenia and anemia are the most common Grade 3 and 4 AEs, and these may be related to concomitant ARV therapy. However, considering that only three of the five subjects with neutropenia received zidovudine, it is possible that raltegravir may also be contributing to the observed declines in neutrophil count.

8.3.4 Drug Related Adverse Events

There were 3 subjects, 1 in Cohort I and 2 in Cohort II with possible drug related adverse events (causality assessment made by the study investigator) during the first 6 weeks. There were no adverse events deemed definitely drug related. All events in Cohort 1 occurred in the raltegravir unexposed cohort.

Table 9 Possibly Drug Related Adverse Events Through 6 weeks

Adverse Events	*Cohort I N= 10 (%)*	*Cohort II N = 26*
Subjects with AE	***1 (10.0)***	***2 (7.7)***
Blood Bilirubin Increased	0 (0.0)	2 (7.7)
Blood Creatinine Increased	0 (0.0)	1 (3.8)
Blood Sodium Decreased	1 (10.0)	0 (0.0)
Cephalohematoma	0 (0.0)	1 (3.8)
Congenital Megaureter	0 (0.0)	1 (3.8)
Inflammation	0 (0.0)	1 (3.8)
Neutrophil Count Decreased	1 (10.0)	0 (0.0)
Pyrexia	1 (10.0)	0 (0.0)
Rhinorrhea	1 (10.0)	0 (0.0)

Source: TRAC.xpt dataset

MO Comment: *There was one subject with drug related laboratory adverse event of Neutrophil Count Decreased in Cohort I. The investigator could not distinguish if the neutropenia was caused by raltegravir or co-administered antivirals; the latter is reasonable given the co-administered anti-retroviral medications. The same subject also experienced blood sodium decreases, pyrexia, and rhinorrhea, all assessed as possibly related adverse events, though clinically this would not be a strong correlation. In Cohort II there were 2 subjects with increased bilirubin. One was Grade I and occurred within the first week, with no recurrence. This subject also had a cephalohematoma since birth which could play a role in increased bilirubin. The other subject with* increased *bilirubin had a Grade 2 event in Week 5 which was preceded by Grade 1 elevated bilirubin in Week 3, making it possible to be drug related. This subject did not have graded elevations in other hepatic enzymes such as ALT, AST, or alkaline phosphatase.*

It is unclear why the other listed adverse events are listed as possibly related to raltegravir, as correlation to cephalohematoma, congenital megaureter, or non-specific inflammation are unlikely. There were no drug related adverse events listed between 6 to 24 weeks in the study.

8.3.5 Dropouts and Discontinuations

In Cohort I, 0 subjects out of 16 discontinued the study drug, whereas in Cohort II there were 3 subjects (11.5%) who discontinued raltegravir prematurely. Only 1 subject discontinued due to AE (Subject 8506734). The other 2 subjects discontinued due to withdrawal of consent. For Subject 8506092, consent was withdrawn due to difficulties with travel to the study site. The subject had no concerning AEs prior to discontinuation (Grade 2 congenital hydronephrosis, Grade 1 creatinine elevation). For Subject 6052991, consent was withdrawn because the family relocated. This subject also had an uneventful course prior to leaving the study, with Grade 1 AST elevation at birth which resolved.

MO comment: *Subject 8506734 in cohort II is a Black female child enrolled at Brazilian site who discontinued the study drug due to AE on Day 31 of life. The reason for discontinuation was a Grade 3 SAE of weight loss. The subject had multiple AEs during the study, all of which resolved: vomiting on day 7 of life; Grade 1 jaundice between Days 8 and 29 days of life with Grade 4 increase in bilirubin on Day 16 of life; Grade 2 Weight loss between Days of life 16-29, and then Grade 3 from Days 29-86, which led to discontinuation. She also experienced Grade 1 oral candidiasis (Days 29-44) and genital candidiasis (Days 37-56). Notable concomitant medications during the study period included nevirapine, zidovudine, fluconazole, and broad spectrum antibiotics. After discontinuation, Grade 4 malnutrition and Grade 3 failure to thrive were noted. The child was ultimately diagnosed with gastroesophageal reflux disease on Day 80; all events resolved. Given the timeframe of raltegravir exposure relative to the adverse events leading to discontinuation and after discontinuation, there is a possible relationship to study drug, though the cause of her adverse events is likely multifactorial. Causality assessment is confounded by other medications and underlying illness may play an additional role.*

8.3.6 Submission Specific Primary Safety Concerns

The study protocol was designed to comprehensively assess clinical and laboratory adverse events including submission specific primary safety concerns as noted from prior adult and pediatric trials such as GI disorders, hepatic toxicity, metabolic disturbances.

Hyperbilirubinemia and jaundice were key safety concerns in the neonatal population, given that drug-related elevations in serum bilirubin coupled with physiologic jaundice could increase the risk of kernicterus and serious neurologic sequelae.

Table 10 Submission Specific Clinical and Laboratory AEs Through 6 Weeks

Dictionary Term	*Cohort I N = 16 (%)*	*Cohort II N = 26 (%)*
Haemoglobin decreased	8 (50)	18 (65.4)
Neutrophil count decreased	9 (56.3)	3 (11.5)
Aspartate amino transferase increased	7 (43.7)	4 (15.4)
Pallor	2 (12.5)	6 (23.1)
Jaundice neonatal	2 (12.5)	5 (19.2)
Blood bilirubin increased	2 (12.5)	5 (19.2)
Blood creatinine increased	1 (6.3)	4 (15.4)
Vomiting	3 (18.7)	1 (3.8)
Blood glucose decreased	1 (6.3)	1 (3.8)
Jaundice	1 (6.3)	1 (3.8)
Blood alkaline phosphatase increased	1 (6.3)	1 (3.8)
Anemia neonatal	1 (6.3)	1 (3.8)
Alanine aminotransferase increased	1 (6.3)	0 (0.0)
Blood albumin decreased	1 (6.3)	0 (0.0)
Blood sodium decreased	1 (6.3)	0 (0.0)

Source: PE6863.xpt and TXW076.xpt dataset

Significant findings include AST increased, Blood bilirubin decreased, Haemoglobin decreased, Jaundice neonatal, Neutrophil count decreased, and Pallor.

Hematologic Disturbances

Overall in Cohort I and Cohort II, anemia and neutropenia are the most common submission specific AEs. As compared to Sponsor tables, MO analysis indicated 1 more neutrophil decreased in the raltegravir-exposed Cohort I group and 3 more in Cohort II; these events were Grade I and 2 in both Cohorts. Relation to study drug is not clearly evident. Findings primarily occurred at Week 1 and Week 2 visits or around Weeks 6-8. There were no notable differences in the frequency of neutropenia and anemia between the Cohort I raltegravir exposed and raltegravir unexposed groups: Neutrophils Decreased was reported in 6 unexposed (60%) and 3 exposed (50%) subjects; Haemoglobin Decreased was reported in 4 subjects in each cohort (40% unexposed and 67% of exposed).

Medical Officer Comment: Low hemoglobin may be multifactorial depending on time of sampling. It may be physiologic directly at birth or at time of physiologic nadir between 6 to 12 weeks of age. Low hemoglobin and a low ANC are also common adverse events with other antiretroviral medications including ZDV, which most subjects were taking. There were 3 subjects with Haemoglobin Decreased (1 in Cohort I unexposed, 2 in Cohort II) who were only on study drug and nevirapine. All other subjects with events of anemia or neutropenia were receiving AZT/ZDV as part of their PMTCT regimen.

Metabolic and Gastrointestinal Disorders

There were no significant findings in regards to metabolic or gastrointestinal disorders in the first 6 weeks of life. Four subjects were noted to have vomiting (all events Grade 1 or 2), which resolved. There was one subject as noted in Discontinuations with weight loss and possible metabolic disorders, that was likely multifactorial in nature. Though not in significant number, decreased blood glucose can be related to ZDV as well.

Elevated Hepatic Transaminases and Hyperbilirubinemia

Concerns for liver function stem from pathway of excretion, enzyme maturation, and risk of kernicterus. A significant number of subjects demonstrated AST elevation, however these were Grade I and Grade II elevations only. In the majority of subjects, AST elevation was not accompanied by ALT elevation, suggesting that the AST elevations may not be due to hepatic injury. Many of the events were reflective of baseline elevations which trended down over time. Most cases of AST elevation (7/11) occurred in Cohort 1 and the majority of those (6/7) occurred in infants who were not exposed to raltegravir in utero.

Medical Officer Comment: There is no discernable trend or association with study drug for hepatic transaminase elevations. The initial elevation is likely a result of either initial hemolysis or birth trauma and can be expected with the age of subjects and trend of both AST and ALT. There is no consistent trend or connection fitting in subjects with elevated hepatic transaminases and clinical AEs like jaundice.

Two subjects in Cohort I had bilirubin elevations: 1 was Grade 1 on Day 39 of age and the other was Grade 2 on Day 35 of age. The latter subject also had non-graded bilirubin elevations between Day 3 and 9 of life, consistent with physiologic increases (serum bilirubin $\geq$10 and <16 mg/dL). Both cases occurred after last dose of raltegravir and self-resolved after one day.

In Cohort II, 1 subject had Grade 4 bilirubin elevation and the remainder with Grade 1 or 2. The onset of graded bilirubin elevations was prior to or at 14 days of age for 3 cases, all Grade 1. The subject with Grade 2 elevated bilirubin had a Grade 1 elevation on Day 18 and Grade 2 on Day 41; however, the subject's actual bilirubin value was trending downward and the increase in toxicity grade was reflective of changes in the cut-offs for grading that are adjusted for age. The Grade 4 bilirubin elevation occurred on Day 16 for the subject who discontinued study therapy due to a clinical AE; this subject's bilirubin was normal at the next visit on Day 23 (see summary of the narrative in Section 8.3.5).

Table 11 summarizes the maximum serum bilirubin values through Day 14 of life for all study participants. No subjects required treatment for hyperbilirubinemia with phototherapy or exchange transfusion.

Table 11: Maximum Bilirubin Value Through Day of Life 14

	Cohort I			Cohort II
	RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)	RAL unexposed (N=26)
	n (%)	n (%)	n (%)	n (%)
<10 mg/dL	9 (90)	5 (83.3)	14 (87.5)	23 (88.5)
≥10 and <16 mg/dL	1 (10)	1 (16.7)	2 (12.5)	3 (11.5)
≥16 mg/dL	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: N = number of neonates in each cohort, n (%) = number (percent) of neonates in each subcategory, RAL = raltegravir

Source: P080 Clinical Study Report, Table 12-13

Subjects with AEs Bilirubin increased, Jaundice, Jaundice neonatal, ALT increased, AST increased were further evaluated and no significant patterns of correlation between these events or directly associated with study drug were found. One subject, 6052741, from the raltegravir unexposed Cohort I group was noted to have Grade 1 jaundice in Week 2 and Grade 2 elevated AST in the first week of life. Subject 8504212 from the raltegravir unexposed Cohort I group and 8505430 from Cohort II were both noted to have AEs of Bilirubin increased and AST increased at least once during the study. Both subjects had Grade 1 or 2 findings. In both subjects AST was elevated at baseline and normalized over subsequent visits. Also for both subjects, serum bilirubin was declining at the time of a graded value, because previous values (although higher) were considered normal for age; Subject 8504212 had Grade 2 bilirubin elevation at Day 35, and Subject 8505430 had Grade 1 increased bilirubin on Day 14. Subject 8506734 in Cohort II was the only subject to have Jaundice and Bilirubin increased both occurring during study. Grade 1 jaundice was noted at birth and in Week 3 assessments, while increased Bilirubin was marked in Week 2 only. The subjects' Bilirubin Increased was rated as Grade 4 on Day 16, with total Bilirubin of 8.01 and direct of 1.43. The levels down trended, and at time of measurement were still below treatment threshold.

Dr. Zvada also performed exposure-safety analyses to determine whether there is a relationship between high raltegravir exposures and risk for hyperbilirubinemia or jaundice. These analyses showed a trend toward a relationship, but interpretation of this finding is confounded by maturation of the UGT1A1-mediated glucuronidation pathway that affects both raltegravir and bilirubin elimination.

Medical Officer Comment: Despite concerns that slow enzyme maturation may exacerbate the risk of severe jaundice in neonates treated with raltegravir, data from this small cohort of subjects is reassuring. However, physicians and caregivers should closely observe babies for jaundice and monitor serum bilirubin values as clinically indicated. No specific recommendations for enhanced laboratory monitoring are warranted at this time based on the study observations.

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

Table 12 Summary of Adverse Events over 24 weeks (Incidence ≥ 4 subjects)

AEs by Preferred Term	*Cohort I N =16 (%)*	*Cohort II N =26 (%)*	*Cohort I &II N=42 (%)*
Haemoglobin decreased	9 (56.3)	20 (76.9)	29 (69.0)
Neutrophil Count Decreased	10 (62.5)	10 (38.5)	20 (47.6)
Aspartate aminotransferase increased	7(43.6)	5 (19.2)	12 (28.5)
Cough	3 (18.8)	8 (30.7)	11 (26.1)
Blood creatinine increased	2 (12.5)	7 (26.7)	9 (21.4)
Nasal congestion	4 (25.0)	5 (19.2)	9 (21.4)
Oral candidiasis	1 (6.25)	8 (30.7)	9 (21.4)
Pyrexia	1 (6.25)	7 (26.7)	8 (19.0)
Jaundice neonatal	2 (12.5)	5 (19.2)	7 (16.7)
Blood bilirubin increased	2 (12.5)	5 (19.2)	7 (16.7)
Vomiting	2 (12.5)	3 (11.5)	6 (14.3)
Congenital umbilical hernia	0 (0.0)	5 (19.2)	5 (11.9)
Rash	1 (6.25)	3 (11.5)	4 (9.5)
Upper respiratory tract infection	0 (0.0)	5 (19.2)	5 (11.9)
Seborrhoeic dermatitis	0 (0.0)	4 (15.4)	4 (9.5)
Congenital syphilis	1 (6.25)	3 (11.5)	4 (9.5)
Pallor	2 (12.5)	2 (7.7)	4 (9.5)

Adapted from PE6863.xpt and TXW076.xpt dataset

MO comment: *Table 12 is a summary of all AEs occurring over 24 weeks with an incidence in at least 4 subjects. Findings of Haemoglobin decreased, Neutrophil count decreased, AST increased, Jaundice neonatal, and Bilirubin increased have been discussed above. Blood creatinine increased was noted predominantly in Cohort II, though with high incidence in Cohort I as well. Only 1 subject in Cohort II was listed as the AE being possibly drug related. There is no clear trend in the subject to indicate creatinine level was related with the drug, therefore medical officer cannot disagree that the elevated creatinine was not drug related. All of the rises in creatinine were listed as Grade I or Grade II and not sustained.*

Pyrexia findings were variable, with some isolated and subjective documented cases. Other cases were clustered with other expected common adverse events such as upper respiratory tract infections and cough. Oral candidiasis is not unexpected in this age group, and did not indicate correlation necessarily with subjects having decrease neutrophil count. Vomiting was not associated with AST, ALT, or bilirubin increase.

8.4.2 Laboratory Specific Adverse Events
All patients on the study underwent complete blood count, HIV-1 nucleic acid testing and resistance testing, chemistries including liver function tests, glucose, electrolytes, creatinine, total and direct bilirubin. Data collected were analyzed for treatment-emergent adverse events, Pertinent laboratory adverse events were listed above in Table 10.

8.4.3 Pediatrics and Assessment of Effects on Growth
There was no formal assessment of effects of raltegravir on growth and development. Overall interpretation of growth in study p080 was limited given lack of longitudinal data. There were no specific adverse events to indicate major impact on growth of pediatric subjects.

8.5 Safety Conclusion
Safety data from IMPAACT study P1110 do not raise any specific safety concerns for use of raltegravir in neonates. However, given the small sample size, close observation is warranted for neonates beginning treatment with raltegravir.

9. Advisory Committee Meeting
An advisory committee meeting will not be held for this efficacy supplement.

10. Pediatrics
This application is in response to PREA PMR 1881-1 to study raltegravir in the neonatal population:

Deferred pediatric study under PREA to evaluate the safety and pharmacokinetics of raltegravir in HIV exposed neonates born to HIV infected mothers. This multiple dose pharmacokinetic and safety study will evaluate raltegravir in addition to the standard of care in HIV exposed neonates from ages to weeks HIV exposed neonates will have safety assessments on or off treatment as appropriate for a minimum of 24 weeks after start of raltegravir therapy.

PMR Establishment Date: March 16, 2012

Final Protocol Submission: December 2012
Final Report Submission: November 2017

The pediatric assessment was presented to the Pediatric Review Committee (PeRC) on November 1, 2017, who agreed with DAVPs recommendation for approval.

The study is also in response to a Pediatric Written Request, which was issued on August 18, 2006 and amended on October 19, 2010 (Amendment #2), November 6, 2014 (Amendment #3), and June 29, 2016 (Amendment #4) to change the timeframe for submitting reports of the studies. The Written Request specified two studies:

- **Study 1:** Multiple-dose pharmacokinetic, safety, and activity study of raltegravir potassium in combination with other antiretroviral agents in HIV-infected pediatric patients.
- **Study 2:** Multiple-dose pharmacokinetic and safety study of raltegravir potassium in addition to the standard of care in HIV-exposed neonates (born to HIV-infected mothers).

Submission of data from IMPAACT Study P1066 fulfilled the requirements for Study 1, and the current submission fulfilled the requirements for Study 2. Pediatric Exclusivity was granted on August 14, 2017.

11. Other Relevant Regulatory Issues

11.1 Inspections

No clinical site inspections were performed. Bioanalytic inspections of the (b) (4) were performed by the Office of Study Integrity and Surveillance (OSIS). In brief, a form FDA 483 was issued at the inspection close-out, with a final inspection classification of Voluntary Action Indicated (VAI). However, a significant objectionable condition was observed that impacted the reliability of a portion of the audited study. Therefore, in accordance with the recommendation of the OSIS review team, censored analyses of the PK data were performed. Exclusion of the data in question did not significantly impact the PK model or study results. Please refer to Dr. Xiaohan Cai's OSIS review and Dr. Zvada's Clinical Pharmacology Review for additional details.

During the review process, DAVP was contacted by the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institutes of Health (NIH) about potential data validation issues identified during a mock EMA inspection in August 2017 which affected IMPAACT study P1110 as well as other trials. DAVP queried Merck regarding the potential impact on the current submission. The Sponsor replied that they had conducted an assessment along with DAIDS, and although deficiencies were noted, Merck found no evidence to suggest an impact on the accuracy of study data or study conclusions. DAVP agrees with Merck's assessment that the integrity of the study data was not compromised.

11.2 Clinical Investigator Financial Disclosure Review

Application Number: 205786

Submission Date(s):

Applicant: Merck

Product: Insentress (raltegravir)

Reviewer: Amol Purandare, MD

Date of Review: November 1, 2017

Covered Clinical Study: A multi-center, phase 1 trial to evaluate the safety and pharmacokinetics of Raltegravir in HIV-1 exposed neonates at High risk of acquiring HIV-1 infection. Study title IMPAACT 1110

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 34 primary investigators who enrolled subjects		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There were no interests/arrangements between the sponsor and its investigators that affected the study outcome; none of the clinical investigators on the study were sponsor employees.

12. Labeling

Labeling negotiations were ongoing at the time this review was finalized. Below are some preliminary proposed modifications to the clinically relevant sections of the label.

1 INDICATIONS AND USAGE
Pediatric Patients:

ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 2 kg.

2 DOSAGE AND ADMINISTRATION
2.3 Pediatrics

- For full-term neonates (birth to 4 weeks [28 days] of age): Weight-based dosing of the oral suspension as specified in Table (b) (4)
  Note: (b) (4) No data are available in pre-term neonates. The use of ISENTRESS is not recommended in pre-term neonates.

Table 5: Recommended Dose for ISENTRESS For Oral Suspension in Full-Term Neonates (Birth to 4 Weeks [28 days] of Age)

Note: If the mother has taken ISENTRESS 2-24 hours before delivery, the infant's first dose should be given between 24-48 hours after birth.

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing †	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily
*The dosing recommendations are based on approximately 1.5 mg/kg/dose. †The dosing recommendations are based on approximately 3 mg/kg/dose.	

6 ADVERSE REACTIONS

HIV-1 Exposed Neonates

In 42 neonates treated with ISENTRESS for up to 6 weeks from birth, and followed for a total of 24 weeks in IMPAACT P1110 *[see Use in Specific Populations (8.4)* (b) (4) , there were no drug related clinical adverse (b) (4) and three drug-related laboratory adverse (b) (4) (one a transient Grade 4 neutropenia in a subject receiving zidovudine-containing regimen for (b) (4) of mother to child transmission (PMTCT), and two bilirubin elevations (one each, Grade 1 and Grade 2) considered non-serious and not requiring specific therapy). The safety profile in neonates was generally similar to that observed in older patients treated with ISENTRESS. No clinically meaningful differences in the adverse event profile of neonates were observed when compared to adults.

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

The doses recommended for neonates (less than 4 weeks of age) *[see Dosage and Administration (2.3)]* (b) (4) Table 15 displays pharmacokinetic parameters for neonates receiving the granules for oral suspension at the recommended dose.

Table 15: Raltegravir Pharmacokinetic Parameters from IMPAACT P1110 Following Age and Weight Based Dosing of the Granules for Suspension

Age (hours/days) at PK Sampling	Dose (See Table 5)	N*	Geometric Mean (%CV†) AUC (mg*hr/L)	Geometric Mean (%CV†) C_{trough} (ng/mL)
Birth – 48 hours	1.5 mg/kg once daily	25	(b) (4) (38.4%)‡	(b) (4) (64.2%)‡
15 to 18 days	3.0 mg/kg twice daily	23	(b) (4) (43.3%)§	(b) (4) (83.7%)§

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.
‡ $AUC_{0\text{-}24hr}$ (N = 24), (b) (4) C_{24hr}, (b) (4)
§$AUC_{0\text{-}12hr}$ (b) (4); C_{12hr}, (b) (4)

17 PATIENT COUNSELING INFORMATION

For Oral Suspension
Instruct parents and/or caregivers to read the Instructions for Use before preparing and administering ISENTRESS for oral suspension to pediatric patients. Instruct parents and/or caregivers that ISENTRESS for oral suspension should be administered within 30 minutes of mixing.

13. Recommendations/Risk Benefit Assessment

- I recommend the approval of this pediatric efficacy supplement.

- Recommended Regulatory Action
  The results from IMPAACT P1110 support approval of raltegravir for the treatment of HIV infection in full-term neonates weighing at least 2kg.

- Risk Benefit Assessment
  Data from IMPAACT study P1110 demonstrate that the proposed neonatal dosing regimen results in mean AUC raltegravir exposures in neonates that are comparable to the targeted adult mean AUC. In addition, the mean C_{trough} concentrations remained above the target. Therefore, the efficacy of raltegravir for the treatment of HIV can be extrapolated from adults to neonates.
  There were no new safety signals for raltegravir. Submission specific concerns of GI disorders, hepatic toxicity, and metabolic disturbances were similar between neonates and adults. Anemia and neutropenia were noted in significant number of subject, however was primarily listed as Grade 1 and 2 events that could be attributed to concomitant medications or physiologic nadir. Although there were concerns about

an increased risk for severe jaundice and kernicterus, no subjects had sustained elevations of serum bilirubin and no subjects required treatment (e.g. phototherapy, exchange transfusion) for hyperbilirubinemia. There were no lasting safety concerns through the follow up period. Approval of raltegravir for use in neonates will add to the armamentarium of HIV medications for HIV infected neonates.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Post market Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will continue to submit Periodic Adverse Drug Experience Reports (PAERs) and Development Safety Update Reports (DSURs) for review

- Recommendation for other Postmarketing Requirements and Commitments
  No additional PMRs or PMCs will be issued in response to this submission

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/s/

AMOL PURANDARE
11/01/2017

PRABHA VISWANATHAN
11/01/2017