CLINICAL PHARMACOLOGY REVIEW

NDA	205786 (S6)
Submission Type	Efficacy Supplement
Submission Date	05/25/2017
Generic Name	Raltegravir
Brand Name	Isentress®
Indication	Treatment of human immunodeficiency virus type 1 (HIV-1)
Dosage Form/ Strength	Granules for oral suspension, 100 mg per single-use packet
Applicant	Merck
Review Team	Simbarashe Zvada, Ph.D.; Jeffry Florian, Ph.D.; Islam R. Younis, Ph.D.

Background

This efficacy supplement contains safety and pharmacokinetics data to support expanding raltegravir indication to include HIV-1 exposed full-term neonates. The applicant submitted pediatric clinical data from the National Institute of Allergy and Infectious Disease (NIAID), Division of Acquired Immunodeficiency Syndrome (DAIDS) pediatric study IMPAACT P1110/ Merck P080 "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 efficacy supplement was submitted in fulfillment of post-marketing requirement (PMR) 1881-1 issued on 3/16/2012 to evaluate the safety and pharmacokinetics of raltegravir in HIV-exposed neonates from ages 0 to 4-6 weeks (born to HIV infected mothers). It also fulfills the Written Request dated 8/18/2006 and subsequent amendments dated 6/27/2007 (amendment #1), 10/19/2010 (amendment #2), 11/06/2014 (amendment #3), and 6/29/2016 (amendment #4).

The Applicant's proposed dosing in full-term neonates is summarized in Table 1 below. 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.

Table 1. The proposed raltegravir oral suspension dosing regimens in full-term neonates (birth to 4 weeks [28 days] of age) (Source: Applicant's label).

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 approximately1.5 mg/kg/dose. †The dosing recommendations are based on approximately 3 mg/kg/dose.	

In support of the proposed dosing regimen, the Applicant submitted:

1. Results from IMPAACT P1110, a Phase 1 study of 42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and weighing ≥2 kg), who received:
   - Either 2 single doses of raltegravir granules for oral suspension within 48 hours of birth and at Day 7 to 10 of age (Cohort I: raltegravir unexposed/exposed neonates)
   - Or a multiple-dose regimen of raltegravir over the first 6 weeks of age (Cohort II: raltegravir unexposed neonates). This regimen utilized similar dosing to the regimen proposed in Table 1.
2. Results from Cohort IV and V of IMPAACT P1066 where raltegravir was dosed at approximately 6 mg/kg every 12 hours:
   - Cohort IV comprised of HIV-1-infected toddlers aged 6 months to < 2 years. Raltegravir was dosed at approximately 6 mg/kg every 12 hours as oral granules for suspension
   - Cohort V had HIV-1-infected infants aged 4 weeks to < 6 months. Raltegravir ~6 mg/kg every 12 hours as oral granules for suspension
3. Results from IMPAACT P1097, study which had mother-neonate pairs enrolled prior to delivery or within 48 hours after birth,
4. A population PK analyses of the available pediatric raltegravir concentration data.

Summary of Clinical Pharmacology Findings

Appropriateness of the proposed dosing regimen

The Applicant's proposed dosing of raltegravir for pediatrics less than one month of age, which is summarized in Table 1, is acceptable. Raltegravir exposures following the administration of the proposed doses in pediatrics are comparable to those exposures observed following the administration of 400 mg dose in adults as summarized in Figure 1, Figure 2 and Table 2.

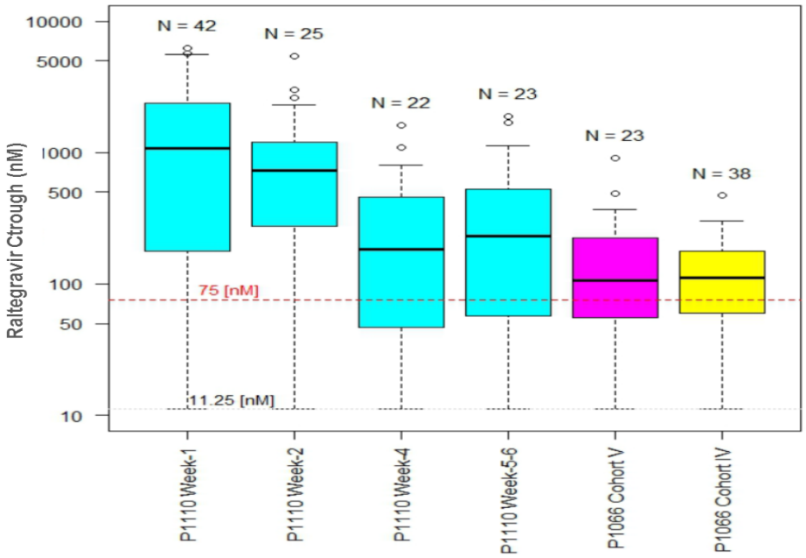


Figure 1. Boxplots of observed trough samples in studies IMPAACT P1110 and IMPAACT P1066. The horizontal dashed red line depicts the minimum Ctrough efficacy target of 75 nM set by the applicant. The regimen used in P1110 was 1.5 mg/kg QD for week 1, 3.0 mg/kg BID for week 2 through 4, and 6.0 mg/kg BID beyond week 4(Source: Applicant's Population PK report, Table 4-12, page 60).

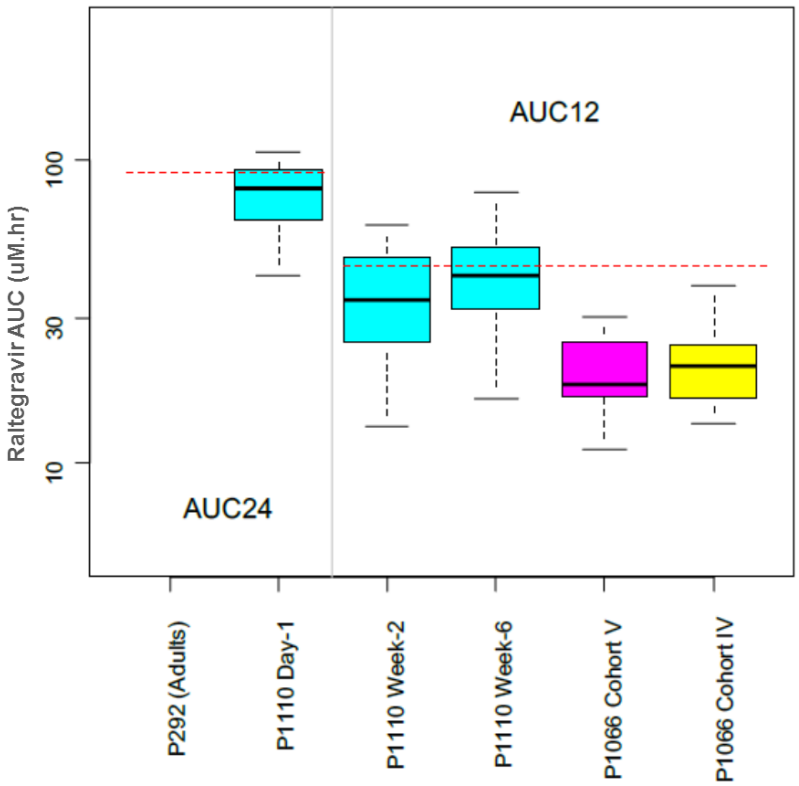


Figure 2. Boxplots of model predicted AUC levels of raltegravir in Studies IMPAACT P1110 and IMPAACT P1066. Horizontal dashed red lines represent the target maximum AUC set by the applicant (90 µM.hr for daily dosing and 45 µM.hr for twice daily dosing). The regimen used in P1110 was 1.5 mg/kg QD for week 1, 3.0 mg/kg BID for week 2 through 4, and 6.0 mg/kg BID beyond week 4. (Source: Applicant's Population PK report, Figure 4-13, page 62).

Timing of first dose in HIV-1 exposed neonates.

The applicant performed simulations to inform the optimal time for first dose in exposed neonates to prevent RAL overexposure in neonates. PK in exposed neonates was simulated assuming various intervals from the time when the last dose was administered to the mother (ranging 2 to 24 hours) to the time of birth. A typical example of these simulations is shown in Figure 3 when a neonate is dosed 36 hours after birth. If the first dose in neonate was changed to 12 hours postpartum, then the AUC_{0-24} of raltegravir in the neonate was predicted to exceed the targeted 90 µM by at most 20%. Overexposure would be reduced if time span between last dose administration to mother and birth is longer. Based on simulations it was determined that the optimal time of administration in neonates is between 24-48 hours after birth in situations where the mother has taken raltegravir 2-24 hrs hours before delivery.

Table 2. Predicted AUC [μM•hr] from different studies and percentages above target AUCs (Source: Applicant's population PK report, Table 4-11, page 64).

	AUC_{0-24}	**AUC_{0-12}**			
	IMPAACT P1110 Cohort II Day-1	**IMPAACT P1110 (Cohort II)**		**IMPAACT P1066**	
		Week 2	**Week 5-6**	**Cohort V**	**Cohort IV**
Minimum AUC	41.6	13.3	16.4	11.1	13.5
25% Percentile	64.8	25.9	32	16.5	16.4
Median	80.3	34.7	41.5	18.3	20.8
75% Percentile	92	47.4	52	25.3	24.7
Maximum AUC	106	60.6	77.9	30.3	38.6
Overexposure (%) AUC_{0-24}: > 90 μM.hr AUC_{0-12}: > 45 μM.hr	33.3	29.2	41.2	0	0
Mean age (range)	0.143 (0, 0.238)	0.944 (1, 2.85)	5.34 (5, 6)	23.6 (5, 52)	62.5 (26, 125)

Bioanalytical Facility Inspection

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of study IMPAACT P1110. A significant objectionable condition was observed during the inspection that impacted the reliability of a portion of the study data. OSIS recommended the omission of a portion of the data from the Agency review. Please refer to OSIS review dated 10/24/2017 for more details. The review team omitted the data from the analysis and the omission of the data did not affect the conclusions of this review.

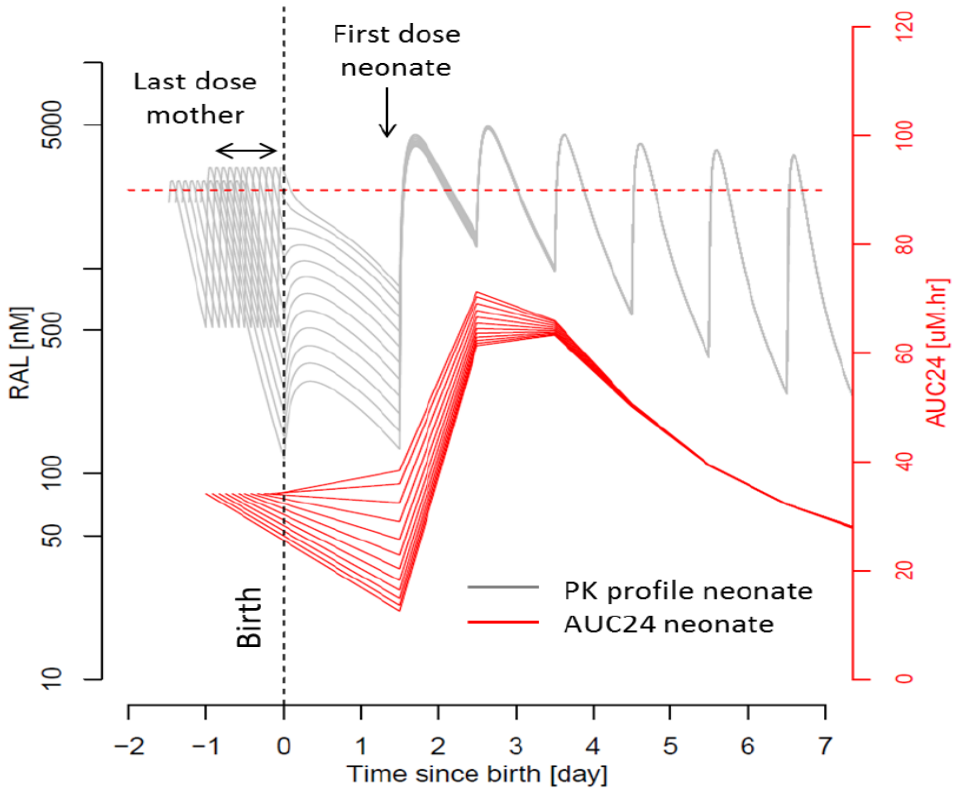


Figure 3. Influence of the time span between the last dose administration to mother and child birth on raltegravir AUC_{0-24} in neonates. The red lines are connected raltegravir AUC_{0-24} in neonates following the administration of raltegravir first dose 36 hrs post-partum. Horizontal dotted line is maximum target AUC_{0-24} at 90 μM.hr proposed by the Applicant. Grey lines represent simulated raltegravir plasma profile in neonates in utero and after birth (Source: Applicant's Population PK report, Figure 4-17, page 68).

Labeling Recommendations

The proposed edits to section 2.3 to include dosing in neonates (Table 1) is acceptable.

Recommendations

The Office of Clinical Pharmacology recommends the approval of raltegravir for the HIV-1 exposed full-term neonates. The applicant fulfilled the PMR 1881-1 and the above mentioned Written Request.

Appendix: Population Pharmacokinetic Review

Applicant's Analysis

The Applicant conducted a population PK analysis for raltegravir following oral administration. The objective of this analysis was to develop a population PK model for raltegravir in raltegravir-unexposed and raltegravir-exposed neonates and infants up to 6 weeks of age, and to use the developed model simulate the exposures in neonates (area under the curve from 0 to 12 hours post dose [AUC_{0-12}], and from 0 to 24 hours post dose [AUC_{0-24}]) in order to find the optimal time of first dose administration in neonates. The estimated exposures in pediatric subjects were compared with estimated exposures in adults. The analysis utilized data from previous reports and new data from clinical trials conducted by the Applicant as described below.

Clinical Studies Included in the POPPK Analysis

The clinical trials which data were used were: IMPAACT P1110, IMPAACT P1066, and IMPAACT P1097 which are detailed below. Table 3 summarizes the subject characteristics of neonates included in the analysis.

Table 3. Subject Characteristics for Subjects with Samples for Inclusion in Pharmacokinetic Analysis (Source: Applicant's Population PK report, Table 4-6, page 48).

Population	Raltegravir-unexposed neonates		Infants		Raltegravir-exposed neonates		Mothers
Merck Study No	P080	P080	P022	P022	P080	NA	NA
IMPAACT Study No	P1110	P1110	P1066	P1066	P1110	P1097	1097
Cohort No	I	II	IV	V	I	1	1
Total number of subjects	10	26	13	11	6	19	19
Number of data points	79	288	121	123	54	75	19
Age range at enrollment	0-2 d	0-2 d	6 mo to < 2 yr	4 wk to < 6 mo	0-2 d	0-1 d	Unknown
Age range for PK sampling	0-11 d	0-6 wk	6 mo to < 2.4 yr	5 wk to < 1 yr	0-11 d	0-2 d	Samples taken < 1 hr postpartum*
Weight range (kg)	2.3-4.2	2.2-5.3	5.5-14	3.7-10.4	2.2-3.4	2.2-4.1	Unknown
Sex (M/F)	4/6	14/12	8/5	7/4	4/2	14/5	0/19

Source: mk0518-pk-neonates-17feb2017.csv
Abbreviations: d: day; F: female; M: male; wk: week; mo: month; yr: year; NA: not applicable; wk: week; yr: year
*Sample of mother of neonate 461350 was taken 2.8 hr postpartum

Study Merck P080/IMPAACT P1110**:** The objectives of the study are:

1. Evaluate the safety and tolerability through 6 weeks of age of raltegravir oral granules for suspension when administered during the first 6 weeks of age with standard prevention of mother-to-child transmission (PMTCT) antiretroviral (ARV) prophylaxis to HIV-1 exposed infants assessed to be at high risk of HIV-1 infection.
2. Evaluate the PK of raltegravir during the first 6 weeks of age.
3. Determine an appropriate dosing regimen of raltegravir oral granules for suspension for use in neonates and infants during the first 6 weeks of age.

Raltegravir was administered per two different regimens, initially defined as follows in Cohorts I and II.

- Cohort I:
    - The primary purpose of Cohort I was generation of PK data that would help inform raltegravir dose selection for Cohort II.
    - Dose Selection:
        - The starting dose was 3 mg/kg which is 25% of the total daily dose (6 mg/kg twice daily) approved for HIV-1- infected infants 4 weeks to <6 months of age. The dose was selected based on interim PK data from study IMPAACT P1097 which showed that raltegravir clearance is substantially lower in the first days of life.
        - The first dose (given <48 hours after birth) provided PK data when infant's glucuronidation is known to be at its nadir, and the second dose (at 7 to 10 days) provided information about changes in metabolism in Week 2. Raltegravir was administered with standard of care ARV for PMTCT prophylaxis.
        - The PK results and safety were monitored to ensure that the individual raltegravir concentrations were in the target range (not exceeding maximum concentration (Cmax) of 8724 ng/mL (19.63 μM) and not exceeding an area under the concentration-time curve from 0 to 12 hours (AUC12) of 28 mg*hr/mL (63.05 μM*hr)) and that there were no life-threatening toxicities probably or related to raltegravir administration.
        - Based on the preliminary PK findings from the first 6 raltegravir-unexposed neonates enrolled in Cohort I, the initial dose of 3 mg/kg was lowered to 2 mg/kg for subsequent raltegravir-unexposed neonates enrolled into Cohort I.
        - Because of the efficient transplacental transfer of raltegravir to infants born to women receiving raltegravir prior to and during delivery, the initial dose of 1.5 mg/kg was selected for the raltegravir-exposed neonates in Cohort I. The second dose at 7 to 10 days of age was unchanged at 3 mg/kg for both raltegravir exposed and unexposed infants.
    - A total of 16 neonates were enrolled in cohort I: 6 neonates exposed to raltegravir in utero and 10 neonates unexposed to raltegravir in utero.
    - Pharmacokinetic sampling for cohort I included the following:
        - Dose 1 (within 48 hours of birth):1 to 2 hours post-dose, 4 to 8 hours post-dose, 12 (±1) hours post-dose, and 24 (±1) hours post-dose.
        - Day 3 to 4 single random PK: one random PK sample was obtained with laboratory evaluations on Day 3 to 4 of age.
        - Dose 2 (7 to 10 days of age) limited PK: Pre-dose, 1-2 hours post-dose and 24 (±1) hours post-dose.
- Cohort II:
    - Raltegravir was administered in addition to standard of care antiretroviral therapy for prevention of PMTCT prophylaxis as follows:

        - Days 1 to 7 (Week 1): **1.5 mg/kg once daily**
        - Day 8 to 28 of age (Weeks 2 to 4): **3 mg/kg twice daily**
        - Days 29 to 42 of age (Weeks 5 to 6): **6 mg/kg twice daily.**
    - A total of 26 neonates unexposed to raltegravir were enrolled in Cohort II.
    - Pharmacokinetic sampling for cohort II included the following (A total of 288 PK samples were available):
        - Entry and after first dose: within 1 hour pre-first dose of raltegravir, then 1 to 2 hours, 6 to 10 hours, and 20 to 24 hours post-dose.
        - After second dose: PK sample obtained 3 to 6 hours post-dose with laboratory evaluations.
        - Days 6 to 9 of age: within 1 hour pre-dose of initiating 3 mg/kg twice daily. A physical exam was also conducted at this visit.
        - Days 15 to 18 of age: within 1 hour pre-dose, then 1 to 2 hours, 4 to 6 hours, and 8 to 12 hours post-dose.
        - Days 28 to 32 of age: within 1 hour pre-dose of initiating 6 mg/kg twice daily.
        - Weeks 5 and 6 of age (days 33 to 42 of age): within 1 hour pre-dose and 3 to 6 hours post-dose.

Study Merck P022/IMPAACT P1066: This was the first study to examine raltegravir in HIV-1 infected children and adolescents. The purpose of this study was to determine the appropriate dose for raltegravir across the pediatric age range from 4 weeks to 18 years of age, by acquiring short and long term safety data, intensive and population PK data, and efficacy experience with raltegravir in HIV-infected children and adolescents. The following 2 cohorts were included in the present analysis:

1. Cohort IV: HIV-1-infected toddlers aged 6 months to < 2 years. Raltegravir dosed at approximately 6 mg/kg every 12 hours using oral granules for suspension.
2. Cohort V: HIV-1-infected infants aged 4 weeks to < 6 months. Raltegravir dosed at approximately 6 mg/kg every 12 hours using oral granules for suspension.

The samples for PK analysis collection included intensive PK (5-12 days after dosing) and sparse PK (Weeks 4, 8, 12 and 24). The intensive PK samples were collected at predose, 0.5, 1, 2, 4 and 12 hr in Cohort IV and predose, 0.5, 1, between 3-5 h and between 8-10 h in Cohort V. The sparse PK samples were collected regardless of food consumption at following time points: Weeks 4 and 12, one sample at 10-14 h post-dose, Week 8, two samples (2 h apart) at 0.5-6 h post-dose, and Week 24, and two samples (2 h apart) at 6-12 h post-dose.

Study IMPAACT P1097**:** The study enrolled 19 mother-neonate pairs and obtained 19 PK samples for analysis of HIV-1-exposed infants. The objectives of the study are:

1. To evaluate the washout PK of raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy
2. To evaluate bilirubin levels and the safety of in utero/intrapartum exposure to raltegravir in infants born to HIV-infected pregnant women receiving raltegravir during pregnancy
3. To develop a neonatal raltegravir dosing regimen to be evaluated in a follow-up study.

Population PK model building

The applicant performed the analysis using NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD) using first-order conditional estimation with interaction (FOCE-I). Graphical analyses were performed using R, Version 3.3.1. All concentrations below the lower limit of quantification (LLOQ) were imputed to half the

LLOQ (5 ng/mL or 11.25 nM) and post dose concentrations below the LLOQ were included in the analysis. Only one individual in the full analysis dataset had 2 consecutive LLOQ measurements, which had negligible impact on the PK model development. Population PK model development was development in 3 stages described below:

1. Design Phase.
   Development of an interim population PK model based on a data set from the first 6 raltegravir-unexposed neonates participating in Study IMPAACT P1110 Cohort I, and supplemented by 24 subjects from Study IMPAACT P1066 Cohorts IV and V. Simulations were also conducted to adjust the dosing regimen in subsequent raltegravir-unexposed neonates and in infants participating in Study IMPAACT P1110 Cohorts I and II, respectively, based on the interim population PK model
2. Model qualification phase.
   This stage included development of a "final population PK model" based on a data set composed of the first 18 raltegravir-unexposed neonates and infants participating in Study IMPAACT P1110 Cohorts I and II supplemented by 24 subjects from Study Merck IMPAACT P1066 Cohorts IV and V. An integrated mother-neonate population PK model combining both raltegravir-unexposed and raltegravir-exposed neonates and infants, and some sparse PK information from mothers was developed to link dosing and exposure in mothers with exposure in neonates following birth.

The integrated model structure

In this model, each mother contributed a single PK data point. The integrated model was therefore composed of two parts, one for raltegravir PK in the fetus/neonate, and one for raltegravir PK in mothers. During pregnancy, central compartments of mother and fetus are linked, reflecting circulation through the placenta and the umbilical cord. Fast exchange rates of 1000 L/h were assumed between the two based on sensitivity analysis, resulting in identical raltegravir concentrations in central compartments. The fetus was assumed to have a body weight as recorded at birth and age of 0 years. The illustration of the integrated model is shown in Figure 4.

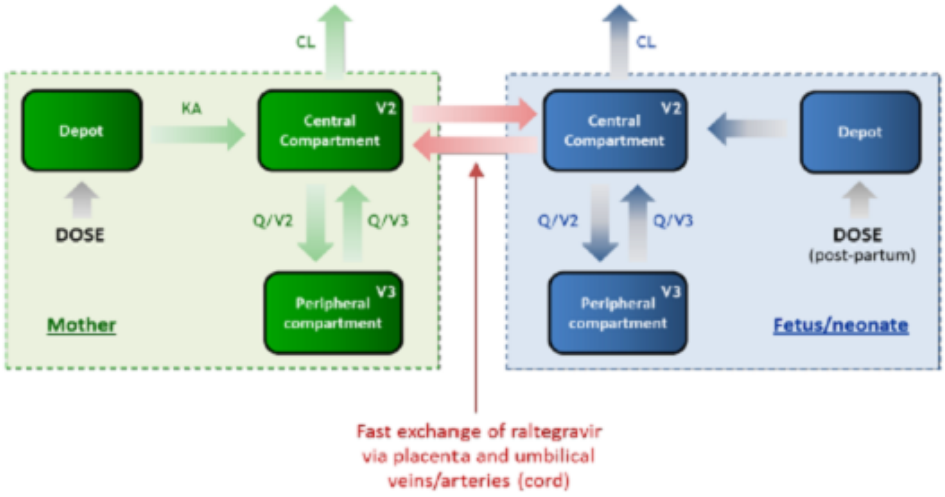


Figure 4. Illustration of the integrated population PK model in mothers and neonates for raltegravir. CL: apparent clearance; KA: first order absorption rate constant; Q: apparent inter-compartmental clearance; V2: apparent central volume of distribution; V3: apparent peripheral volume of distribution (Source: Applicant's Population PK report, Figure 4-9, page 50).

Bioanalytical Method

Quantitative determination of raltegravir in human plasma was accomplished using a liquid extraction and high-performance liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection. The calibration

curve was linear over the range of 1 – 3000 ng/mL and the mean multiple correlation coefficient was 0.9992 ± 0.0002. The mean relative error (% dev) was within the range of -3.3 to 4.2 %. The coefficient of variation (% CV) ranged from 0.6 to 2.9 %. The performance of the bioanalytical method is acceptable.

Results

The final parameter estimates using all the data are shown Table 4 while the diagnostic plots are shown in Figure 5.

Table 4. Parameter estimates after bootstrapping (1000 replicates) of the final raltegravir integrated population PK model. (Source: Applicant's Population PK report, Table 4-8, page 51).

		Final model 205			Bootstrap result		
Parameter	**Unit**	**Population prediction**	**Lower 95%CI**	**Upper 95%CI**	**Median**	**P2.5**	**P97.5**
OFV	--	10859.88	NA	NA	10847.64	10244.87	11417.48
Neonate (Raltegravir-unexposed & Raltegravir-exposed)							
V2	L	7.03	5.05	9.78	7.16	4.85	9.91
V3	L	10.4	8	13.3	10.3	7.37	13.4
CLMAX	L/hr	9.44	7.44	11.4	9.34	7.44	11.8
Q	L/hr	0.787	0.559	1.11	0.8	0.538	1.2
KAMAX	1/hr	0.43	0.306	0.555	0.452	0.315	0.875
CLtau	1/yr	11.3	7.56	15.1	11.3	7.38	15.9
KAbase	1/hr	0.0916	0.0344	0.244	0.0876	0.0216	0.247
KAtau	1/yr	63.2	1.4	125	60.8	6.7	135
IIV on CL	--	0.33	0.108	0.552	0.314	0.132	0.483
IIV on KA	--	0.196	0.103	0.289	0.178	0.0802	0.291
Mother							
KA	1/hr	0.175	0.0888	0.261	0.178	0.0576	0.42
F	--	0.517	0.404	0.631	0.527	0.381	0.734
IIV on F	--	0.311	0.0834	0.538	0.283	0.101	1.01
Residual error							
RUV-prop	--	0.54	0.498	0.582	0.536	0.489	0.577
RUV-add	nM	11.9	9.11	14.7	11.6	9.95	40.9

Abbreviations: CI95 low: lower limit of the 95% confidence interval; CI95 high: upper limit of the 95% confidence interval; CLbase: typical value of apparent clearance at birth; CLMAX: maximum increase in apparent clearance from CLbase; CLtau: first order rate constant for the age-related changes in apparent clearance; F: oral bioavailability mother; F4: oral bioavailability neonate (after birth); IIV: inter individual variability; KAbase: typical value of absorption rate constant at birth; KAMAX: maximum increase in absorption rate constant from KAbase; KAtau: first order rate constant for the age-related changes in absorption rate constant; Q: typical value of apparent intercompartmental clearance; RUV-add: additive term of the residual error; RUV-prop: proportional term of the residual error; V2: typical value of apparent central volume of distribution; V3: typical value of apparent peripheral volume of distribution. Note: Typical values of clearances and volumes refer to a subject weighing 25 kg

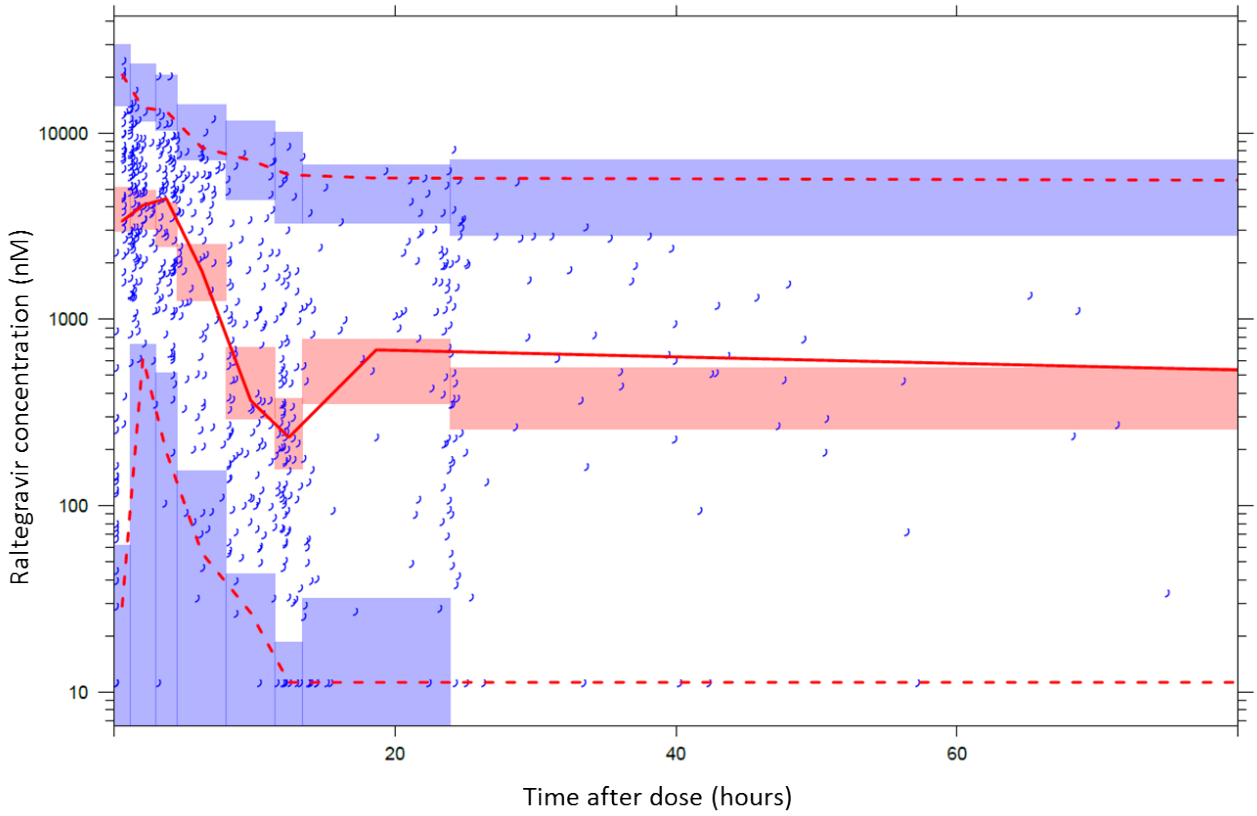


Figure 5. Visual predictive check for raltegravir integrated model. Solid red line is the median of the observed data. Dashed red line is the upper and lower limits of the 95% range of the observed data. Red blocks are the 95% prediction interval for the simulated median data. Blue blocks are the 95% prediction interval for the upper and lower limits of the 95% range (Source: FDA analysis).

Simulations for AUC comparisons

The applicant used AUC_{0-12}, AUC_{0-24} and Ctrough for comparison of the adequacy of dosing regimens. Ctrough was maintained above the minimum target efficacy threshold of 75 nM for the proposed dosing (Figure 1). Figure 2 and Table 2 show that the AUC_{0-24} (AUC24) falls below 90 µM.hr and the AUC_{0-12} (AUC12) below 45 µM.hr for the proposed dosing..

Timing of first dose in HIV-1 exposed neonates.

The applicant performed simulations to inform the optimal time for first dose in neonates exposed to HIV-1 prior to birth in situations where the mother was administered raltegravir. Simulations results are shown in Figure 3. Generally, if time span from last dose administration to mother prior to birth is less than 6 hours, the neonate PK time course profile was predicted to decline; if the time span was more than 6 hours, the profile was predicted to initially rise due to back flow from the neonate peripheral compartment as illustrated in Figure 6. Overexposure would be reduced if time span between last dose administration to mother and birth is longer than 6 hrs. As illustrated in Figure 3, the applicant demonstrated that if a first dose in neonate is 36 hours post-partum and the mother has received her last dose 2 to 24 hours before giving birth, the AUC_{0-24} of raltegravir in the neonate was predicted to stay below the upper limit of 90 µM.hr (40 µg.hr/mL). If the assumption of first dose in neonate was changed to 12 hours postpartum, then the AUC_{0-24} of raltegravir in the neonate was predicted to exceed 90 µM.hr (40 µg.hr/mL) by at most 20% for not more than 2 days. Based on these

simulations, the optimal time of administration in neonates if the mother has taken raltegravir 2-24 hrs hours before delivery is between 24-48 hours after birth.

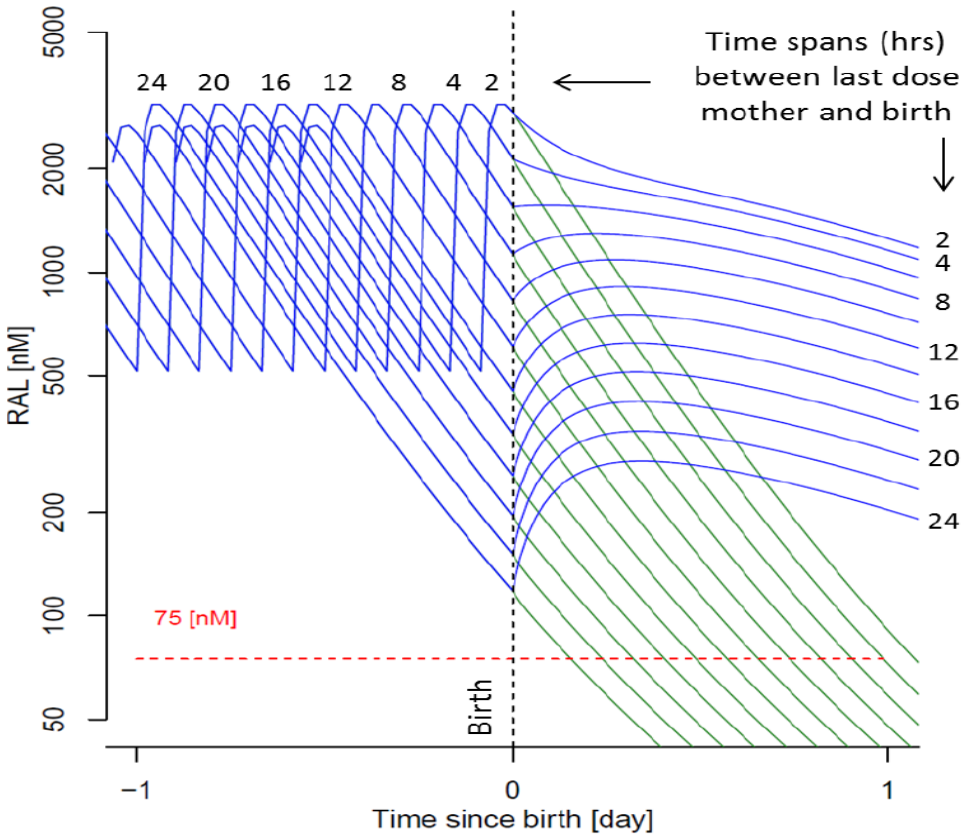


Figure 6. Simulated Concentration-Time Profiles of Raltegravir in both Mother (green) and Neonate (blue), with Last Dose Administration in time range 2 – 24 hours prior to birth (times denoted on the figure). (Source: Applicant's Population PK report, Table 4-15, page 66).

Reviewer's Comments

Generally, the population pharmacokinetic model developed by the applicant is acceptable based on an assessment of the provided diagnostic plots. The pharmacokinetic model and simulations performed by the Applicant provide supportive information for the proposed raltegravir dosing in pediatrics 0 to 4 weeks of age.

It should be noted that higher exposures were observed in neonates during the first week of birth. There were incidences of elevated bilirubin levels, but no causal trend could be established. This may be due to variability, limited sample size, or factors entirely separate from raltegravir exposure. As such, the observation does not necessitate any dose adjustments or additional monitoring beyond that which would be performed as part of routine clinical practice.

Reviewer's Independent Assessment

Introduction

During the raltegravir review, it was identified that a subset of samples could not be considered reliable because of an inspection conducted by OSIS. The primary objective of the reviewer's analysis was to evaluate whether removal of these samples from the Applicant's population PK analysis had any impact on the modeling results and dosing recommendations. In addition, the reviewer conducted exploratory exposure-response analyses to assess the relationship between raltegravir exposure and the incidence of jaundice / neonatal jaundice in study P1110.

Methods

The datasets and characteristics of patients used in the analyses are summarized in the Table 3. The source of dataset and files used in the analysis are summarized in Table 5.

Table 5. Source for dataset and files used in the analysis

Description	File name	EDR Location
Final raltegravir model	run205-mod.txt	\\CDSESUB1\evsprod\NDA205786\0081\m5\datasets\04mhp6\analysis\legacy\programs
Population PK datateset	mk0518-pk-neonates-17feb2017.xpt	\\CDSESUB1\evsprod\NDA205786\0081\m5\datasets\04mhp6\analysis\legacy\datasets

Dataset

The original dataset included 85 individuals with 759 observations across all studies. Based on the OSIS inspection, it was recommended to remove a total of 37 samples from 5 subjects, all of whom were infants from study P1110 and were previously exposed to raltegravir in utero. This amounts to approximately 5% of the observations. Thus, the dataset used for the reviewer's population PK was comprised of 84 individuals with 722 observations. The characteristics of individuals with impacted PK samples, the total number of PK samples in those individuals, and the number of impacted PK samples are summarized in Table 6.

Methods

The reviewer utilized the same population PK model developed by the Applicant for this analysis. To evaluate the impact of removing some of the PK dataset, the following items were compared between the model with all data and the final model after removing 37 observations: final parameter estimates, goodness of fit plots, individual plots (not shown) and VPCs (not shown).

Table 6. Characteristics of individuals with PK data excluded based on the OSIS inspection.

Item	Individuals affected				
	7055316J	**8505999J**	**8506691H**	**6052991E**	**8506173E**
Cohort	1	1	2	2	2
Age range sampling	0-11d	0-11d	0-6 wk	0-6 wk	0-6 wk
Dose (mg)	8	4; 8	4; 8; 20; 25	5; 10; 30	5; 8; 28
Number of observations	9	9	13	13	13
Removed observations	6	9	10	2	10

The relationship between raltegravir exposure and jaundice / neonatal jaundice was explored graphically using model predicted AUC (over 24 hours). Exposures were summarized for those patients with and without events of interest. Univariate logistic regression was conducted to visually assess any trend between raltegravir exposure and jaundice / neonatal jaundice events.

Results

Population PK analysis

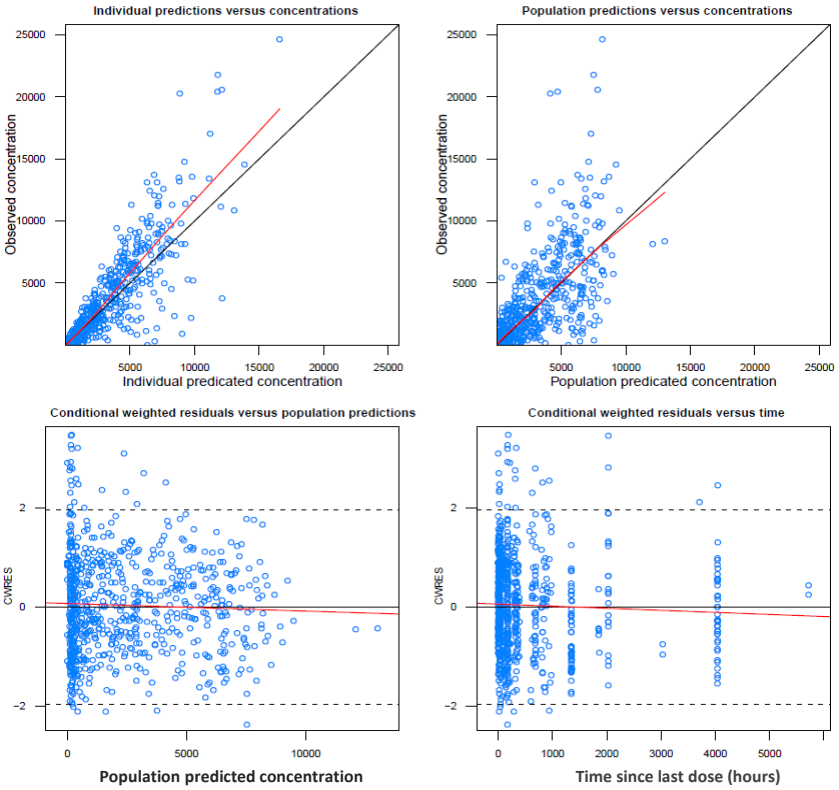
The comparison of parameter estimates between the two models is shown in Table 7 while model diagnostic plots for both assessment is shown in Figure 7.

Table 7. Comparison of parameter estimates between model with all PK data (run211) and model with reduced data set with PK samples removed based on OSIS recommendations (run212).

Parameter	**run211 (Applicant; full data set)**		**run212 (reviewer; reduced data set)**	
	Estimate	**%RSE**	**Estimate**	**%RSE**
Mother				
Ka (1/hr)	0.175	29%	0.192	28.50%
F1	0.517	15.80%	0.502	13.60%
V2 (L) - (fixed)	3.52		3.52	
V3 (L) – (fixed)	27		27	
CL (L/hr) –(fixed)	9.73		9.73	
Q (L/hr) – (fixed)	0.866		0.866	
Neonate (Raltegravir-unexposed and Raltegravir-exposed)				
V2 Central (L)	7.03	8.90%	6.96	9.30%
V3 Peripheral (L)	10.4	5.70%	10.2	6.10%
CLMAX (L/hr)	9.45	12.80%	9.54	12.20%
Q (L/hr)	0.787	74.60%	0.799	89.30%
KAMAX (L/hr)	0.43	14.90%	0.432	16.90%
CLtau (1/yr)	11.3	18.20%	11.3	18.80%
Kabase (1/hr)	0.0916	21.30%	0.0973	23.60%
Katau (1/yr)	63.3	51.70%	61.6	46.60%
IIV_F1	0.311	44.40%	0.254	43.30%
IIV_CL	0.329	32.20%	0.324	33.60%
IIV_ Ka	0.196	24.60%	0.197	24.40%
Residual error				
RUV-add	11.9	11.60%	12.7	19.40%
RUV-prop	0.54	4%	0.543	4.20%

Abbreviations: Ka: first-order absorption rate constant; F1: oral bioavailability neonate (after birth); V2: typical value of apparent central volume of distribution; V3: typical value of apparent peripheral volume of distribution; CL: apparent clearance; Q: typical value of apparent intercompartmental clearance; CLMAX: maximum increase in apparent clearance from CLbase; KAMAX: maximum increase in absorption rate constant from Kabase; CLtau: first order rate constant for the age-related changes in apparent clearance; IIV: inter individual variability reported as variance; Kabase: typical value of absorption rate constant at birth; Katau: first order rate constant for the age-related changes in absorption rate constant; RUV-add: additive term of the residual error; RUV-prop: proportional term of the residual error; Note: Typical values of clearances and volumes refer to a subject weighing 25 kg.

Run211



Run212

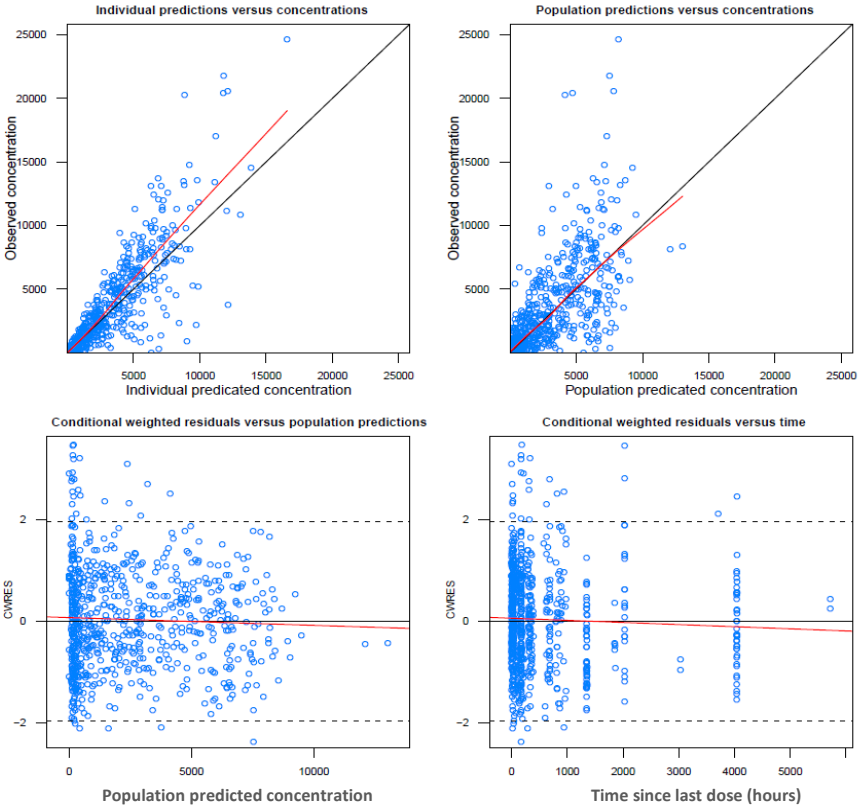


Figure 7. Goodness of fit plots for run211 (Applicant; full data set) and run212 (reviewer; reduced data set with PK samples removed based on OSIS recommendations).

Conclusion

Removing the subset of PK samples, as recommended by OSIS due to inspection issues, had no significant impact on the parameter estimates for the model nor on model diagnostics. Hence, excluding the identified PK samples does not affect the results of this analysis nor the dosing recommendations proposed by the Applicant.

ER evaluation for safety

The neonates who were reported to have high bilirubin or jaundice / neonatal jaundice were seven and nine, respectively, out of forty-two neonates who participated in study P1110. There was a slight difference in AUC between those with jaundice / neonatal jaundice compared to those without (Figure 8 and Figure 9). The difference in AUC for those with and without high bilirubin was very small (Figure 10). Further analysis explored the probability of developing jaundice using logistic regression during the first week after birth. A very minor trend in probability of jaundice was obtained with increased raltegravir exposure (Figure 11), suggesting that there could be other factors which contributed to jaundice/neonatal jaundice observed.

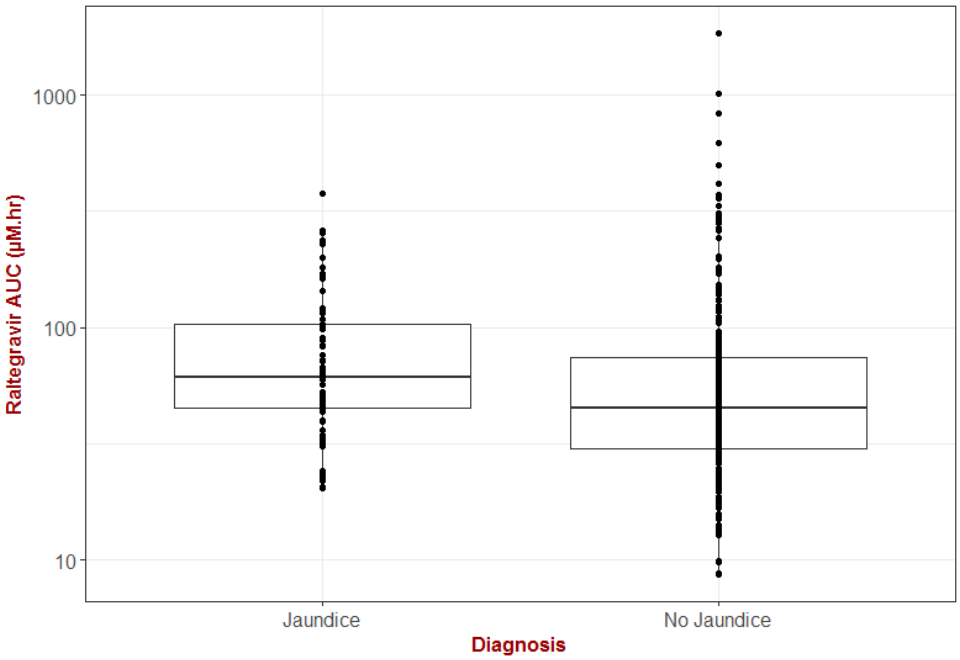


Figure 8. Box plot of difference in AUC between neonates who had neonatal jaundice and those without jaundice.

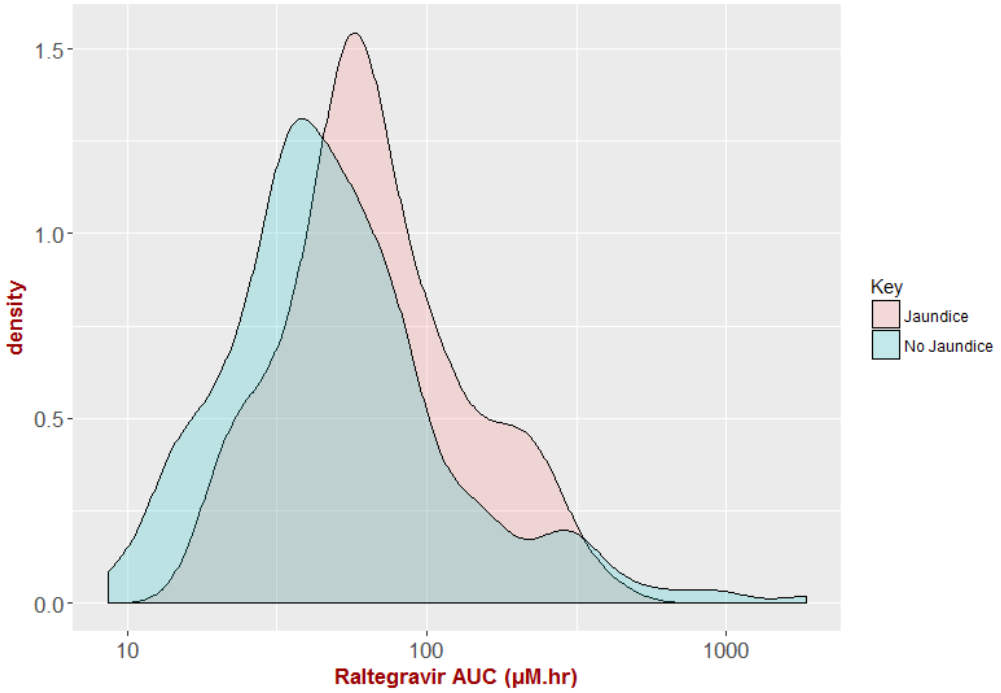


Figure 9. Density plot of raltegravir AUC stratified on jaundice status

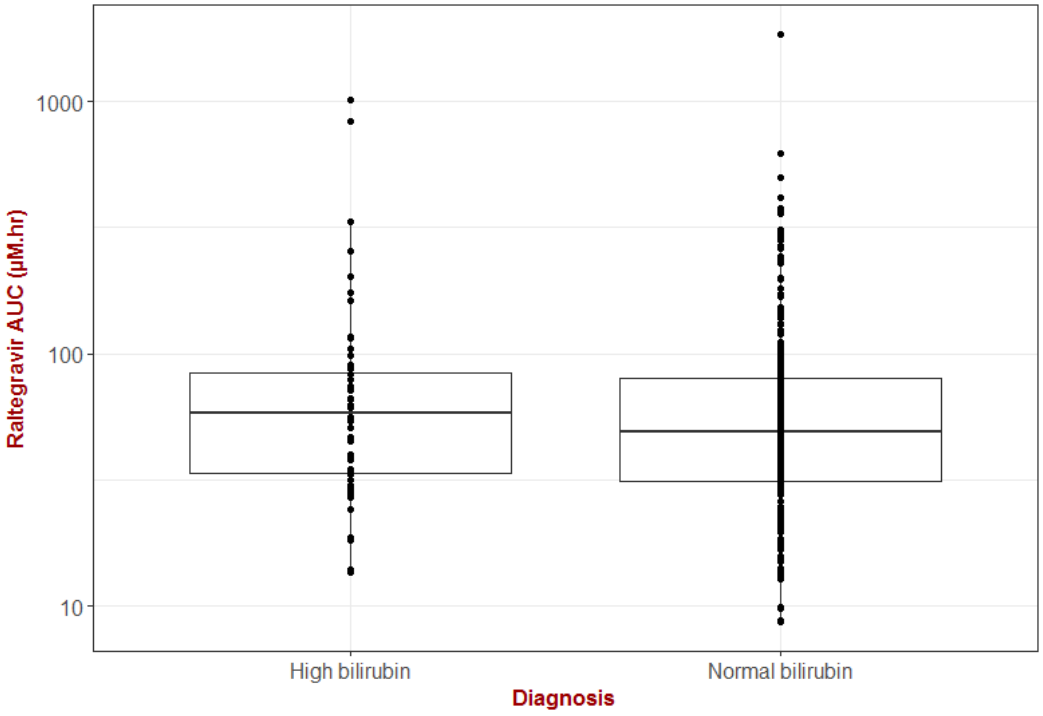


Figure 10. Box plot of difference in AUC between neonates who had high bilirubin and those with normal bilirubin.

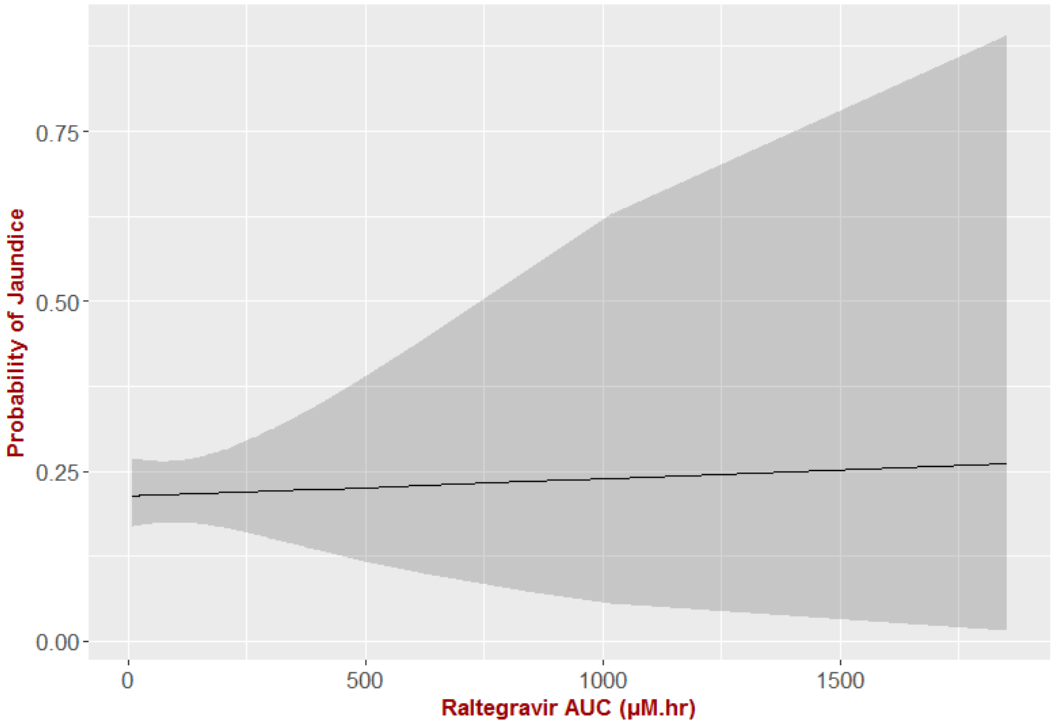


Figure 11. Logistic regression representing the probability of experiencing jaundice/neonatal jaundice as a function of raltegravir AUC. The gray shaded area represents 95% confidence interval.

Conclusion

There were no observed trends with regards to raltegravir exposure. The high exposures observed in the first week of birth was neither associated with high bilirubin levels nor with jaundice / neonatal jaundice.

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/s/

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