22 February 2018
EMA/163887/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Isentress

International non-proprietary name: raltegravir

Procedure No. EMEA/H/C/000860/II/0064/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ARV	Antiretroviral
BW	Body weight
CI	Confidence interval
Cmax	Maximum concentration
Cmin	Average concentration
CV%	Percent coefficient of Variation
GFS	Granules for suspension
HIV	Human immunodeficiency virus
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
INSTI	Integrase strand transfer inhibitor
PK	Pharmacokinetics
PMTCT	Prevention of Mother-to-Child Transmission
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase 1A1 isoform

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 24 May 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA, IIIB and A

Extension of indication (for Isentress 100 mg granules for oral suspension) to include treatment of HIV-1 exposed full-term neonates (under the age of 4 weeks) based on safety and PK data from one pivotal Phase 1 study, IMPAACT P1110 (Protocol 080), in a total of 42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and ≥2000 g), who received either 2 single doses of oral suspension, within 48 hours of birth and Day 7-10 of age (Cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (Cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly.
The provision of the study (IMPAACT P1110) addresses the final PIP measure, i.e. Study 4, conducted to generate PK, safety, and tolerability data in HIV exposed neonates and infants <6 weeks of age born to HIV infected mothers.

Further, the MAH proposed to update the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurement of the smaller doses required for neonates. As a consequence, there was a need to replace the 5 mL syringe supplied in the current commercial kit with 3 new oral dosing syringes, and sizes (1 mL, 3 mL, and 10 mL), from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC have been updated and the labelling and instructions for use in the Package Leaflet and the Annex A have been updated accordingly.

An updated RMP version 12.0 was submitted as part of the application.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet, Labelling and Annex A and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0155/2016 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0155/2016 was completed. The PDCO issued an opinion on compliance for the PIP P/0155/2016.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	24 May 2017
Start of procedure	12 August 2017
CHMP Rapporteur Assessment Report	2 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	18 October 2017
Updated PRAC Rapporteur Assessment Report	19 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 November 2017
Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur Assessment Report	23 January 2018
PRAC Rapporteur Assessment Report	25 January 2018
PRAC members comments	30 January 2018
Updated PRAC Rapporteur Assessment Report	10 February 2018
PRAC Outcome	8 February 2018
CHMP members comments	13 February 2018
Updated CHMP Rapporteur Assessment Report	13 February 2018
Opinion	22 February 2018

2. Scientific discussion

2.1. Introduction

This Application supports the use of raltegravir in human immunodeficiency virus type 1 (HIV-1) exposed full-term neonates, and is based on the results of a single study conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), Protocol 1110 (also known as MSD Protocol 080; hereafter referred to as IMPAACT P1110).

Following completion of the line extension application EMEA/H/C/00680/X/44G, granules for oral suspension were added to the already available adult and chewable paediatric tablets. The granules for oral suspension were (and currently still are) indicated for use in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in children, toddlers and infants from the age of 4 weeks. The recommended doses for infants from 4 weeks and children of < 25 kg are as follows:

Body weight (kg)	**Volume (dose) of suspension to be administered**	**Number of chewable tablets**
3 to less than 4	1 ml (20 mg) twice daily	
4 to less than 6	1.5 ml (30 mg) twice daily	
6 to less than 8	2 ml (40 mg) twice daily	
8 to less than 11	3 ml (60 mg) twice daily	
11 to less than 14†	4 ml (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 ml (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25		1.5 x 100 mg‡ twice daily

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily (see section 5.2).

† For weight between 11 and 20 kg either formulation can be used.

‡ The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

Each single-use sachet contains 100 mg of raltegravir which is suspended in 5 ml of water giving a final concentration of 20 mg per ml and the recommended volumes are administered using a 5-mL syringe, with or without food.

At the time of completion of EMEA/H/C/00680/X/44G, the SmPCs for the adult (400 mg) and chewable paediatric tablets (25 mg or 100 mg) the indications and posology sections were amended to reflect extension of use down to 4 weeks of age and to advise prescribers of the availability of alternative formulations, including the fact that the adult tablets, chewable tables and GFS are not bioequivalent. Data were added to sections 4.8, 5.1 and 5.2 in each SmPC.

2.2. Quality aspects

The scope of this application is to extend the approved indication for Isentress granules for oral suspension to include the neonatal population (under the age of 4 weeks). For ease of dosing, as part of this variation the MAH proposed to revise the suspension volume so that the 100 mg sachet was to be suspended in 10 mL (vs. the current 5 mL) for a final suspension concentration of 10 mg/mL (vs. the current 20 mg/mL), to facilitate accurate measurement of the smaller doses required for neonates.

The recommended doses for the product were therefore amended to fit the neonatal population, and consequently new measuring/administration devices must be introduced as the currently approved

device is now inadequate for this population. To facilitate both the larger suspension volume and the range of dosing including dose recommendations for neonates, the Applicant will replace the 5mL syringe supplied in the current commercial kit with 3 new oral dosing syringes sizes (1 mL, 3 mL, and 10 mL).

The new syringes will be provided by a new supplier, Comar LLC. Sections 3.2.P.7 and 3.2.R have been amended accordingly.

This consequential change in suspension volume from 5 mL to 10 mL, and the new oral dosing syringes, has been incorporated into the dosing instructions in the product information texts, and in the revised instructions for use to be supplied with the marketed product in a booklet format, going forward.

The granules for suspension are presented in sachets and co-packaged with the device constituents and ancillary components into a kit, which is the commercial presentation – see Table below:

Table 1. Components of the Kit

Kit Components	Component Type
60 sachets filled with granules for suspension (100 mg/sachet)	Drug constituent
Two 1mL Oral dosing syringes	Device constituent
Two 3 mL Oral dosing syringes	
Two 10 mL Oral dosing syringes	
Two mixing cups	Ancillary component
Literature	Labeling components

The dossier has been updated to include supporting data for the new oral dosing syringes and data are presented below:

Mixing Cup

The granules for suspension are intended to be constituted within the provided mixing cup. 10 mL of water that has been measured with the supplied 10 mL oral syringe described in Sec. 3.2.P.7 is added to the cup. The sachet contents are then added to the cup. The user is intended to then close the cup lid and gently swirl the mixture until a homogeneous mixture has been created. The appropriate dose is then drawn into the syringe for administration. The cup is constructed of polypropylene resin that meets regulatory and compendial requirements as shown in Sec. 3.2.P.7. In-use stability studies were done by transferring the contents of a sachet into a mixing cup, adding 10 mL of water, dispersing the powder and holding the suspension in the mixing cup for two hours under ambient room temperature conditions as described in Sec. 3.2.P.8.1.

Change of Mixing Implements from Clinical Trials

Constitution of ISENTRESS (raltegravir) for oral suspension performed as part of clinical trials used different components than will be included in the commercial kit. The clinical trial implements consisted of a mixing cup and a spatula. After the water diluent and contents of the foil laminate sachet were placed into the cup, the spatula was used to stir the mixture until a homogeneous suspension is formed. The mixing implement that will be included in the commercial kit is a nominal 20 mL polypropylene cup with an attached tight-fitting lid that is snapped into place to seal the cup. Suspension constitution is carried out by gently swirling the sealed cup until a visually homogeneous

suspension is formed. The mixing cup lid is then opened to allow the oral syringe to be inserted for withdrawal of the proper dose volume.

The combination of the new mixing implement and the new constitution method is an improvement from the clinical trials because one less component is handled and washed, the constitution process is simpler, and has a lower risk of accidental suspension spillage.

Switching from the mixing implements is considered acceptable because:

- The cups are made of similar resins that meet compendial and regulatory requirements.
- Compatibility of the suspension with the new cup has been established through simulated in-use testing as part of stability studies, data from which are shown in section 3.2.P.8.1 and 3.2.P.8.3.
- Extractable assessment of the new mixing cup concluded the materials are safe for patient.
- An acceptable homogeneous suspension can be created using either type of implement
- The design of the new cup with a lid allows it to be washed and re-used multiple times, as was also the case with the implements employed in the clinical trials
- The mixing cup is not used for dispensing a dose or measuring. Accordingly, there are no graduations or measurement markings on the mixing cup. Performance testing confirmed the mixing cup can be used up to 60 times.
- Withdrawal of the constituted suspension into the dosing syringe is carried out in the same manner

Oral Syringes

Oral syringes will be supplied as part of the commercially marketed kit. The 10-mL syringe is intended to be used both to measure the water that is used to create the suspension and potentially deliver the dose. The user will draw water into the barrel to the 10mL mark printed on the syringe barrel. The water is expelled into the open mixing cup and the sachet contents are added to the mixing cup. The user will then close the cup lid and gently swirl the mixture. After the suspension has been prepared, the 1 ml, 3 ml or 10 mL syringe will be used to draw in the prescribed volume of suspension from the mixing cup. The details of the oral syringes are provided in section 3.2.P.7 and functional testing in 3.2.P.2.2.

Oral Syringe Extractables and Compatibility Assessment

The instructions for use specify that constituted Raltegravir Granules for Suspension be dosed within 30 minutes after constitution with water. The suspension comes in contact with the mixing cup during the mixing stage of the suspension preparation and with the oral syringe during dosing. The materials of construction of the mixing cup and the oral syringes meet food contact regulations (Section 3.2.P.7). Compatibility and in-use testing have demonstrated acceptable compatibility with both the mixing cup and oral syringes used.

Additionally, an extractable assessment concluded the syringes are safe for patient use demonstrating acceptability after 60 uses and washes.

Following preparation in the mixing cup, the suspension comes in contact with the oral syringe during dosing. A 1 mL, 3 mL, or 10 mL syringe may be used for dosing. The suspension was tested for assay and degradation products immediately after preparation and after being drawn into and held under

ambient room temperature conditions in each of the three syringe types for two hours. No change in assay or degradation products was observed over the two-hour period.

The acceptable assay and degradation products results obtained after holding the suspension separately in the mixing cup and in each of the oral syringes that may be used for dosing (1 mL, 3 mL, 10 mL) for two hours under ambient room temperature conditions demonstrates acceptable compatibility for the 30-minute in-use period specified in the instructions for use.

Oral Syringe Dose Accuracy and Uniformity Assessment

ISENTRESS (raltegravir) for oral suspension is supplied with dosing syringes (Section 3.2.P.2.7) with respective graduations of:

- 1 mL = 0.1 mL graduations starting at 0.1 mL to 1 mL
- 3 mL = 0.25 mL graduations starting at 0.5 mL to 3 mL
- 10 mL = 0.5 mL graduations starting at 1 mL to 10 mL

A study was performed to demonstrate that the dosing devices comply with the Ph. Eur. monograph 2.9.27, “Uniformity of mass of delivered doses from multidose containers” and provide acceptable dose volume accuracy.

One lot of each syringe size was used in the test:

- 1 mL dosing devices
- 3 mL dosing devices
- 10 mL dosing devices

A suspension was prepared using a representative batch of ISENTRESS (raltegravir) for oral suspension. Using this suspension, each of the three syringe sizes was tested at the volumes that may be dosed with that syringe type for the recommended dose for ISENTRESS (raltegravir) for oral suspension in neonates and paediatric population.

Results of the study were provided and met the acceptance criteria stated in Ph. Eur. monograph 2.9.27. The results also met the acceptance criterion established for volume accuracy that the delivery volume accuracy tolerance of the oral dosing syringe must be no greater than ±10% of the intended volume.

The Instructions for Use (IFU) for ISENTRESS OS states that after use in dosing of the oral suspension, the syringe barrel and plunger are to be washed with warm water and dish soap, rinsed with water, and allowed to air dry. A single syringe may be used and washed up to 60 times over the course of use of an ISENTRESS OS Combination Product Kit. Due to this, an additional Dose Accuracy/Uniformity study was designed to use washed syringes. The syringes tested were manipulated and washed the equivalent of 60 times. The volumes evaluated for each syringe represent the lowest and highest volumes that may be dosed with a specific syringe type in accordance with the proposed age and weight based dosing table in conjunction with the IFU. Results of the washed syringe study results met the acceptance criteria stated in Ph. Eur. monograph 2.9.27 and met the acceptance criterion established for volume accuracy that the delivery volume accuracy tolerance of the oral dosing syringe must be no greater than ±10% of the intended volume.

The current shelf life for ISENTRESS Oral Suspension (OS) is 24 months when stored at the specified conditions. Thus, a Dose Accuracy/Uniformity study was also performed using representative syringes over two years in age in conjunction with a representative batch of ISENTRESS OS of similar age. As stated previously, a single syringe may be used and washed up to 60 times over the course of use of

an ISENTRESS OS Combination Product Kit. Due to this, the aged syringes were manipulated and washed the equivalent of 60 times prior to testing. The volumes evaluated for each syringe represent the lowest and highest volumes that may be dosed with a specific syringe type in accordance with the proposed age and weight based dosing table in conjunction with the IFU. Results of the washed aged syringe study were provided. These results met the acceptance criteria stated in Ph. Eur. monograph 2.9.27 and remained within the specified delivery volume accuracy tolerance of the oral dosing syringe studied.

The results demonstrate acceptable accuracy and uniformity of delivered doses for the oral dosing syringes (1 mL, 3 mL, 10 mL) to be included in the ISENTRESS OS Combination Product Kit. Acceptable accuracy and uniformity has been demonstrated for syringes when first received from the vendor, for syringes that have been subjected to manipulation and washing simulating normal use and for syringes over two years in age that have also been subjected to manipulation and washing.

2.2.1. Discussion on quality aspects

The commercial container closure system supported by the development studies described for ISENTRESS (raltegravir) for oral suspension is a heat-sealed foil laminate sachet.

Control strategies have been put in place to ensure the drug product is maintained within acceptable temperature and humidity ranges as defined by the product characterization study. These control strategies include drug substance and excipient moisture in-process controls, environmental and procedural controls in manufacturing, storage and packaging areas, well defined storage and use restrictions, and an appropriate container closure system. No changes in product quality are anticipated during long term product storage or short-term excursions from labelled storage conditions due to the application of the noted control strategies.

This is supported by the data reported for the FSS batches in Sec. 3.2.P.8.3. These results clearly show that the container closure system is adequate for long-term storage of the drug product. No changes in assay, degradation products, dissolution, moisture or appearance were seen at any storage temperature for up to 48 months.

The accessories included with the drug product, that is, the mixing cup and oral syringes, have been shown to be appropriate to perform their intended purpose when used according to instructions, allowing the user to properly constitute the drug product, measure the appropriate suspension volume, and administer the measured dose.

Device Constituents: Oral Dosing Syringes/Dispensers

Oral dosing syringes/dispensers from the manufacturer are considered Class I medical device with measuring function. These syringes have been assessed with respect to the conformity assessment procedure described in Article 11.5 and Annex V (Module D1) of Council Directive 93/42/EEC on Medical Devices, as amended, for the aspects of manufacture concerned with the conformity of the products with metrological requirements, as amended, and found to comply. The CE certificate and EC declaration of conformity (DOC) for all the three syringe sizes are provided in Section 3.2.R.

Representative schematic drawings and photos for the oral dosing syringe from a typical supplier have been provided.

The new oral syringe barrels are all composed of the same translucent polypropylene which is compounded with a polypropylene slip agent. The opaque plunger rods for the 1 mL, 3 mL and 10 mL syringes are composed of high density polyethylene; the 1 mL plunger rod has a white colorant; the 3 mL plunger rod has a green colorant; and the 10 mL plunger rod has a blue colorant.

Safety aspects

The syringes comply with Commission Regulation (EU) n°10/2011 as amended repealing Directive 2002/72/EC within the framework defined by the Regulation (EC) n°1935/20004 provided the finished product meets the applicable migration limits. The manufacturer of the syringes has confirmed that the raw materials used in these products do not contain DEHP (Diethylhexylphthalate) or related phthalates.

The barrel and plunger rods meet the applicable requirements for food contact of the US Code of Federal Regulations Title 21 Parts 177.1520 (c) Specifications 3.1a (barrel), 2.1 and 2.2 (plunger rods). The slip agent meets the applicable US Code of Federal Regulations Title 21 Parts 174.5, 177.1520 (c) 3.1a and 178.3860.

The white colorant material is “generally recognized as safe” (GRAS) prior sanctioned, and is subject to an effective Food Contact Notification (FCN), Threshold of Regulation (TOR), or identified in one or more of the following sections of Title 21 of the Code of Federal Regulations 177.1520, 178.3297, 178-2010.

The green colorant material is composed of ingredients comply with sections 174.5, 177.1520 (c) 3.1a, 178.2010, 178.3297 and 184.1229 of Title 21 of the Code of Federal Regulations subject to any applicable restrictions described herein and in Title 21 of the Code of Federal Regulations.

The blue colorant material is composed of ingredients that are cleared by the U.S. Federal Food and Drug Administration (FDA) for use in Polyethylene as described in sections 174.5, 177.1520 (c) 3.1a and 178.3297 of Title 21 of the Code of Federal Regulations.

Compatibility

The suspension comes into contact with the oral dosing syringe during dosing. The dwell time is brief and materials meet the food contact regulations. Compatibility and in-use testing demonstrated acceptable compatibility.

Quality Control Information

Upon receipt of the components, an initial inspection is carried out to verify Purchase Order requirements and evaluation of supplier Certificates of Analysis (COA)/Certificates of Compliance (COC). The MA holder may accept all or part of the quality control test results based on review of the Supplier Certificates of Analysis (COA)/Certificates of Compliance (COC) provided the supplier has demonstrated reliability.

2.2.2. Conclusions on quality aspects

The data presented to support the new oral dosing syringes is acceptable and the conditions for Type IAIN (Cat. B.IV.1.a.1) have been fulfilled. The dossier has been updated to include supporting data.

The CE certificate and EC declaration of conformity (DOC) for all the three syringe sizes have been provided in Section 3.2.R (Notified Body Number 0434; dated 13/01/19). Representative schematic drawings and photos for the oral dosing syringes have been provided.

Satisfactory details of the components/composition of the new oral dosing syringes have been provided. Satisfactory data have been provided to demonstrate that the syringes are compatible with the medicinal product and can deliver the required doses accurately in line with the proposed posology. Studies have also been presented on dosing accuracy and uniformity of mass delivered using syringes

washed up to 60 times as well as aged syringes with product at end of shelf-life; results presented are satisfactory.

The proposed new oral dosing syringes are considered appropriate for use with the proposed posology.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant provided a nonclinical overview to justify the lack of any new data and to discuss the relevance of existing data to the current application for use in the first 4 weeks of life. In summary, the application is supported by the completed nonclinical studies, including those conducted in neonatal animals, to support use of the raltegravir 400 mg BID regimen.

The rat, a species recommended in the ICH Nonclinical Testing Guidelines, was chosen as a preclinical toxicology species for raltegravir development and was used in juvenile and pre- and post-natal studies. The absorption, metabolism, and excretion profiles of raltegravir are similar in rats and humans. All pivotal studies with raltegravir were supported by toxicokinetic measurements either within the study or from separate studies conducted under the same conditions and using identical doses administered in the same vehicle. All pivotal nonclinical toxicity studies were conducted consistent with ICH Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations.

2.3.2. Pharmacology

No new nonclinical pharmacodynamics (PD) studies have been conducted to support this application. Findings from in-vitro studies previously conducted in support of the raltegravir 400 mg BID regimen also pertain to this application as they are independent of the formulation, frequency of its administration or developmental age of targeted clinical population. These studies included a comprehensive evaluation of the in-vitro antiviral and biochemical properties of raltegravir. In antiviral assays, raltegravir demonstrated activity in HIV-1 infected T-lymphoid cells (IC95= 31 ± 20 nM), was active against reverse transcriptase and protease resistant viruses and demonstrated additive to synergistic activity in combination with other anti-retroviral agents. Raltegravir at 10 µM or greater showed no marked off-target inhibitory activities against a counter screen assay panel of 166 human proteins including enzymes, transporters and receptor-ligand interactions. The safety pharmacology studies demonstrated that raltegravir evoked no meaningful effects when evaluated on a diverse range of physiological functions (cardiovascular, neurobehavior, respiratory) in vivo or in vitro.

2.3.3. Pharmacokinetics

No new nonclinical pharmacokinetic (PK) studies have been conducted to support this application. The nonclinical pharmacokinetic studies provided a comprehensive ADME evaluation in rats and dogs, metabolism in CD-1 mice and in-vitro evaluations of raltegravir as a substrate and inhibitor of major human P450 (CYP) and UGT) enzymes and as inducer of major CYPs. Protein binding, metabolism and excretion of raltegravir in humans were also assessed. In addition, the inhibitory effect of raltegravir on major human drug uptake and efflux transporters was evaluated.

Raltegravir is eliminated primarily by metabolism via UGT1A1-mediated glucuronidation, with urinary excretion being the minor pathway. The ontogeny of UGT1A1 enzyme in the neonatal and paediatric population, and how the maturation of UGT1A1 activity progresses from birth, has been studied by quantifying the activity of UGT1A1 in fetal and paediatric liver samples using bilirubin activity assays. Results of these studies indicate that UGT1A1 activity toward bilirubin is nearly undetectable in the

fetal liver and that catalytic activity increases progressively after birth, reaching adult levels sometime around 3 to 6 months of age. These findings suggest that maturation of UGT1A1 activity may likely influence raltegravir disposition in neonates and therefore it was included as a factor in the population PK models used to make dosing recommendations for raltegravir in neonates.

Co-administration of potent UGT1A1 inhibitors or inducers may alter plasma levels of raltegravir. Potential effect of the UGT1A1 maturation process on the profile of raltegravir as the victim of DDIs in neonates is not known. In vitro, raltegravir does not inhibit (IC50>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A or induce CYP1A2, CYP2B6 and CYP3A4.

In addition, raltegravir is not a strong inhibitor (IC50>50 µM) of the UGTs tested (UGT1A1, UGT2B7) or the major human drug efflux and uptake transporters in vitro. Raltegravir does not inhibit P-glycoprotein and inhibits only 22% of BCRP-mediated transport at 100 µM. Raltegravir does not inhibit OATP1B1, and it shows only 40% inhibition of OATP1B3 and 16% inhibition of OCT1 at 100 µM in vitro. Raltegravir also does not inhibit OCT2 and is not a strong inhibitor of OAT1 and OAT3 (IC50 of 108 µM and 18.8 µM, respectively) and MATE1 and MATE2-K (52% and 29% inhibition at 100 µM, respectively) in vitro. Based on in-vitro data, raltegravir has overall a low propensity to perpetrate clinically meaningful DDIs with substrates of major drug metabolizing enzymes or drug transporters at plasma concentrations following administration of recommended doses in neonates (mean Cmax of 6.4 µM following 3 mg/kg BID administration; estimated unbound Cmax of 1.1 µM).

2.3.4. Toxicology

The nonclinical toxicology programme consisted of in-vitro and in-vivo studies to assess genotoxicity, acute oral toxicity and toxicokinetic studies in rats, dogs and mice, sub-chronic and chronic studies of up to 27 weeks duration in rats and 53 weeks in dogs, developmental and reproductive toxicity studies in rats and rabbits (including assessment of placental and lactational transfer and potential for neonatal/juvenile toxicity in rats) and two year bioassays in rats and mice for assessment of carcinogenicity potential. There was no potential relevant toxicity, specific hazard in developmental or reproductive studies, genotoxicity or carcinogenicity identified. Raltegravir was shown to be present in the milk of lactating rats orally administered raltegravir.

In neonatal and juvenile aged rats an initial exploratory dose range-finding study was conducted by daily oral administration of raltegravir from Postnatal Day (PND) 5 to Postnatal Week (PNW) 9. The rats were randomized into 5 groups of 16 females and 16 males each that received 150, 300, 450, or 600 mg/kg/day of raltegravir suspended in polyethylene glycol 400 in deionized water vehicle (80:20, w/w) or vehicle only. Assessment of toxicity was based on mortality, clinical observations, body weights and clinical pathology examinations. The only test article-related change was slightly decreased mean serum glucose values in males of the 450 and 600 mg/kg/day groups. Toxicokinetics were performed on the study. When considering inter-animal variability across doses, Cmax was similar across the dose range and AUC0-24 was approximately dose proportional between 150 and 300 mg/kg/day and similar between 300 and 600 mg/kg/day (maximum feasible dose). Based on these results, a high dose level of 600 mg/kg/day was selected for the subsequent definitive juvenile toxicity study in rats.

In the definitive GLP juvenile toxicity study, the potential effects of raltegravir on growth and behaviour in rats, including histomorphology, was assessed following oral administration from PND 5 to PNW 8. The reversibility of the potential effects of raltegravir was evaluated in a 6-week treatment-free period. Plasma concentrations of raltegravir and the glucuronide metabolite (L-001277512) were determined in PNW 7. Rats were assigned to 4 groups of 43 or 44 pups per sex (11 fostered litters per group) that received 50, 200 or 600 mg/kg/day of raltegravir suspended in polyethylene glycol 400 in deionized water (80:20, w/w) or vehicle only, once daily by oral gavage on PND 5 to PNW 8 (PND 52

to 54). There was no evidence of toxicity based on mortality, physical signs, body weights, developmental signs, haematology, serum biochemistry (including glucose values), ophthalmologic examination, behavioural assessments and reproductive performance, including embryonic/fetal survival. No treatment-related gross findings or organ weight changes were noted at either the interim or final (recovery) necropsy.

Treatment-related histomorphologic changes in the stomach were observed in mid- and high-dose animals. Treatment-related vacuolation of the non-glandular stomach epithelium was observed at ≥200 mg/kg/day in both males and females. This change was confined to non-glandular epithelium adjacent to the limiting ridge and was frequently associated with increased numbers of the resident inflammatory cell population consisting of neutrophils, eosinophils and lesser numbers of lymphocytes and plasma cells.

Increased inflammation was observed at ≥200 mg/kg/day in males and at 600 mg/kg/day in females, which consisted of increased numbers of resident inflammatory cell population (neutrophils, eosinophils and lesser numbers of lymphocytes and plasma cells) that was most prevalent subjacent to the limiting ridge, and often extended into the adjacent mucosa of the glandular stomach. No treatment-related gross or histomorphologic changes were observed in the stomach following cessation of treatment for approximately 6 weeks (final recovery evaluation), thus indicating complete recovery. Systemic exposure (AUC) and Cmax values for raltegravir and the glucuronide metabolite L-001277512 were similar for animals in this juvenile toxicity study compared to animals in previous studies with mature rats.

Treatment-related stomach findings consisting of vacuolation of the non-glandular stomach epithelium adjacent to the limiting ridge with increased numbers of the resident inflammatory cell population was observed and attributed to local irritation effects resulting from the oral raltegravir formulation. The no-observed-adverse effect level (NOAEL) was ≥600 mg/kg/day (AUC0-24 67 µM•hr and Cmax 50.1 µM, approximately 1.5-fold above the AUC0-24 and 12-fold above the Cmax achieved in neonatal patients administered raltegravir) based on the local non-glandular stomach irritant effect without relevance to humans, as humans do not have a non-glandular stomach region or limiting ridge. Findings in juvenile rats were consistent with the stomach irritation effects seen in adult rats and juvenile rats were therefore considered to be equally sensitive to the stomach inflammation seen in adult rats dosed with raltegravir. There were no additional toxicities noted in juvenile rats indicating that, overall, raltegravir effects were similar between juvenile and adult rats.

2.3.5. Ecotoxicity / environmental risk assessment

The environmental risk assessment for raltegravir was recently evaluated as part of the extension application for granules for oral suspension (EMEA/H/C/000860/X/0044/G), using the maximum allowable daily dose of 1600 mg/day (adults co-administered with rifampin).

Using all default values for market penetration and no removal in the environment, the Predicted Environmental Concentration (PEC) is determined to be 8 µg/L. The maximum daily dose of raltegravir associated with this filing is 300 mg/day which corresponds to a PEC of 1.5 µg/L.

Therefore, predicted environmental concentrations are anticipated to be equal to or lower than those already approved. No significant increase in the environment is expected to occur as a result of this application.

2.3.6. Conclusion on the non-clinical aspects

No additional nonclinical data are being submitted within this application and none are required. Some of the most relevant data have been described above. All other nonclinical data have been fully assessed in prior submissions. The nonclinical studies support the use of raltegravir in the neonatal population.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Phase and Country	Study Title	Trial design	Dosing regimen	Trial population	Subject exposure
Phase 1 United States, Brazil, South Africa	A Phase 1 Trial to Evaluate the Safety and Pharmacokinetics of Raltegravir in HIV-1-Exposed Neonates at High Risk of Acquiring HIV-1 Infection	Open-label, parallel, non-comparative	Raltegravir oral suspension Cohort I: 1.5 to 3 mg/kg raltegravir x1 at birth and 3 mg/kg x1 at 7-10 days using GFS Cohort II- 1.5 mg/kg QD raltegravir for Week 1; 3 mg/kg BID for Week 2 to 4; 6 mg/kg BID for Week 5 and 6 using GFS.	Males/females: 22/20 Age: birth to 48 hours of age Neonates born to HIV-1 infected mothers	Cohort I: 16 (6 exposed to raltegravir in utero, 10 unexposed raltegravir in utero) Cohort II: 26 (all unexposed to raltegravir in utero)

2.4.2. Pharmacokinetics

The GFS formulation used in i) IMPAACT P1066 (P022; the study that supported use from 4 weeks of age in X44G), ii) IMPAACT P1110 [P080], in which raltegravir was administered to neonates, and iii) the biocomparison study PN068 is the same GFS formulation currently approved for use in infants at least 4 weeks of age and weighing at least 3 kg. This application to extend use from birth applies to the exact same GFS formulation as currently approved.

Study P080 [IMPACT P1110] - Study Title*: 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 was an open label uncontrolled study of raltegravir in neonates born to HIV-infected mothers. The study enrolled subjects at 13 sites across three countries between 2014 and 2016.

Objectives

Primary Objectives:

1. To evaluate the safety and tolerability through 6 weeks of age of raltegravir (GFS) when administered during the first 6 weeks of life with standard PMTCT antiretroviral prophylaxis to HIV-1-exposed infants assessed at high risk of HIV-1 infection.
2. To evaluate the PK of raltegravir in the first 6 weeks of life along with standard PMTCT antiretroviral therapy prophylaxis.
3. To determine an appropriate dose of raltegravir GFS for use in neonates and infants during the first 6 weeks of life.

Secondary Objectives:

1. To assess safety and tolerability of raltegravir through 24 weeks of age when administered during the first 6 weeks with standard PMTCT antiretroviral prophylaxis.
2. To investigate the relationship between neonatal raltegravir elimination and UGT1A1 genotype and whether there is an association of UGT1A1 (*28/*28) and SLCO1B3 (rs2117032-C/T) with hyperbilirubinaemia. These associations were to be assessed with Fisher's exact test. The power of these statistical tests depended upon the distributions of the variables to be analysed, and was extremely limited due to the small sample size. Therefore, the test was not performed.

Study participants

Maternal Inclusion Criteria

1. Mother was known to have been HIV-1 infected prior to delivery or in the immediate postpartum period. Documentation of HIV-1 infection was defined as positive results from 2 samples (whole blood, serum or plasma) collected at different time points, including results in the clinical record from past testing. The mother-infant pair was to be enrolled so that the infant received the first raltegravir dose within 48 hours of birth.

Sample #1 could have been tested by non-CAP/CLIA-approved laboratory or non-study public or President's Emergency Plan for AIDS Relief programmes. If FDA-approved methods were not available, test methods were verified to be in accordance with GCLP and approved by the IMPAACT Central Laboratory. Sample #1 was tested using any of the following:

a. Two rapid antibody tests from different manufacturers or based on different principles and epitopes.

b. One EIA OR Western Blot OR immunofluorescence OR chemiluminescence

c. One qPCR or bDNA (>5,000 copies/mL)

d. One HIV DNA PCR

e. One qualitative HIV RNA PCR

f. One HIV culture (prior to August 2009)

g. One total HIV nucleic acid test

Sample #2 was to be performed in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operated according to GCLP guidelines and participated in an appropriate external quality assurance programme (for international sites). Sample #2 was tested using any of the following:

a. One EIA confirmed by Western Blot OR immunofluorescence OR chemiluminescence

b. One quantitative HIV RNA PCR or bDNA (>5,000 copies/mL)

c. One HIV DNA PCR

d. One qualitative HIV RNA PCR

e. One HIV culture (prior to August 2009)

f. One total HIV nucleic test

2. Mother was at high risk of transmitting HIV-1 to infant as evidenced by any of the following:

a. Mother had not received any ART during the current pregnancy prior to the onset of labour

b. HIV RNA >1000 copies/mL within 4 weeks before delivery

c. Receipt of ART for <4 weeks 28 days before delivery

d. On ART for ≥4 weeks, but had not taken any drug for >7 days prior to delivery

e. Mother had known documented multi-class drug resistant virus

Note: Mothers might have received prenatal and/or intrapartum antiretrovirals.

3. Maternal written informed consent for study participation.

Maternal Exclusion Criteria

1. Known maternal-fetal blood group incompatibility

2. Mother received raltegravir as part of her cART regimen after delivery and intending to breastfeed

3. Mother received raltegravir prior to and through delivery unless last raltegravir dosing during prenatal period was >7 days prior to delivery (Cohort I infants only). By protocol amendment this exclusion criterion was modified during the study to allow enrolment in Cohort I of up to 6 mother-infant pairs in which the mother had received raltegravir during pregnancy and through delivery. Therefore, subgroups exposed to raltegravir in utero (raltegravir-exposed neonates) and not exposed to raltegravir in utero (raltegravir-unexposed neonates) were to be included in this cohort but not in Cohort II.

Infant Inclusion Criteria

1. HIV-1-exposed full-term neonates aged ≤48 hours. Infant might have received up to 48 hours of standard of care ART before enrolment

2. Gestational age at birth at least 37 weeks

3. No known severe congenital malformation or other medication condition not compatible with life or that would have interfered with study participation

4. Birth weight ≥2 kg

5. Able to take oral medications

6. Parent or legal guardian able and willing to provide signed informed consent.

Infant Exclusion Criteria

1. Bilirubin exceeding the AAP guidelines for phototherapy

2. Clinical evidence of renal disease such as oedema, ascites, or encephalopathy

3. Receipt of disallowed medications (phenytoin, phenobarbital, rifampicin)

Treatments

All neonates received raltegravir GFS. After reconstitution in 5 mL the suspension concentration was 20 mg/mL. By protocol amendment #3 the suspension volume was increased to 10 mL for a final concentration of 10 mg/mL to facilitate administration of the lower doses required. The raltegravir dosing regimens were selected based on meeting PK targets for safety and efficacy. A minimum of 12 neonates were to be enrolled into Cohort I to provide PK data that would inform raltegravir dose selection for Cohort II. Drug regimens, administration, and duration for Cohort I and Cohort I are as follows:

Cohort I: HIV-1-exposed full-term neonates (aged ≤48 hours) initially received:

- Raltegravir GFS 3 mg/kg as a single dose within 48 hours of birth in addition to PMTCT prophylaxis
- A second single dose of raltegravir GFS 3 mg/kg on day 7-10

Modifications of the dosing regimen were made during the study (see above re modified maternal inclusion criteria and below for explanation of the dose modifications):

- For raltegravir-unexposed infants, those first enrolled received the 3 mg/kg initial dose but subsequently the initial dose was lowered to 2 mg/kg
- For raltegravir-exposed infants the initial dose was 1.5 mg/kg

The second dose was 3 mg/kg in all Cohort I infants.

The first dose within 48 hours of birth provided PK data when infant glucuronidation is known to be at its nadir while the second dose (7 to 10 days) provided information about changes in metabolism in Week 2.

Since raltegravir clearance was substantially lower in the first days of life based on interim data from IMPAACT P1097 (an ongoing study in infants born to HIV-infected pregnant women receiving raltegravir 400 mg BID) the 3 mg/kg single dose was selected to minimize potential safety concerns and still provide informative PK data. The 3 mg/kg single starting dose of raltegravir represented 25% of the total daily dose (6 mg/kg BID) studied in HIV-1-infected infants 4 weeks to <6 months of age in IMPAACT P1066 and currently approved for this age range.

The study was designed to allow raltegravir dosing to be modified in the range of 1.5 mg/kg to 6 mg/kg per dose. The PK results and safety were assessed through team monitoring at least every 4 weeks and at full cohort accrual to ensure that the individual raltegravir concentrations did not exceed a Cmax of 8724 ng/mL (19.63 μM) and did not exceed an AUC0-12 of 28 mg*hr/L (63.05 μM*hr). These targets were based on mean exposure in the raltegravir QTc study 024 in adults.

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. Furthermore, because of the efficient transplacental transfer of raltegravir to infants born to women receiving raltegravir prior to and during delivery (P1097; see above), the initial dose of 1.5 mg/kg was selected for the infants exposed to raltegravir in utero.

Cohort II: HIV-1 exposed full-term neonates (aged ≤48 hours) received raltegravir GFS in addition to PMTCT prophylaxis as follows:

- 1.5 mg/kg once daily during Days 1 to 7 of age (week 1)

- 3 mg/kg twice daily during Days 8 to 28 of age (weeks 2 to 4)

- 6 mg/kg twice daily during Days 29 to 42 of age (weeks 5 and 6)

The weights used to determine dose were obtained entry visit (target within 48 hours of birth), day 6 to 9 and day 28 to 32. The dose to be used for week 5 and 6 was the approved dose of 6 mg/kg BID.

The dosing regimen reflected the modelling and simulation analysis, and was revised from the original protocol prior to opening of Cohort II in amendment #2.

The PK targets for Cohort II were those used in P1066, with adjustment for once daily dosing. IMPAACT P1066 BID doses were selected such that the PK profile of raltegravir resembled that attained in adults dosed with 400 mg BID. In Cohort II, the PK safety target was GM-AUC-based, and depended on whether the drug was dosed once (AUC0-24) or twice (AUC0-12) daily. The PK efficacy target was GM trough concentration and was the same for once daily and twice daily dosing (GM C24 and C12, respectively). The PK targets for Cohort II were:

- Once-daily dosing: GM AUC24 12 to 40 mg*h/L (28 to 90 µM*hr) and an approximate GM trough (C24) >33ng/mL (75nM)

- Twice-daily dosing: GM AUC12 6 to 20 mg*h/L (14 to 45 µM*hr) and an approximate GM trough (C12) >33ng/mL (75nM)

Raltegravir was to be provided to infants if needed for treatment of documented HIV-1 infection through the protocol for the duration of the study as part of cART. The choice of ART regimen was at the discretion of the site investigator.

Raltegravir Compassionate Use (Cohorts I and II)

At the end of the study, HIV-1-infected infants who continued to receive raltegravir as part of their cART regimen were to have access to the raltegravir through MSD's Paediatric Compassionate Use Program until GFS became commercially available.

Outcomes/endpoints

Evidence of HIV-1 infection and resistance testing (Cohorts I and II)

All infants received appropriate testing for evidence of HIV-1 infection within 48 hours of birth (if not done as per standard of care) and at 6 and 24 weeks of age. If any infant was found to be HIV-1 infected during the study, blood samples for viral resistance testing to raltegravir and other antiretroviral therapies were to be collected as soon as possible after confirmation of vertical transmission.

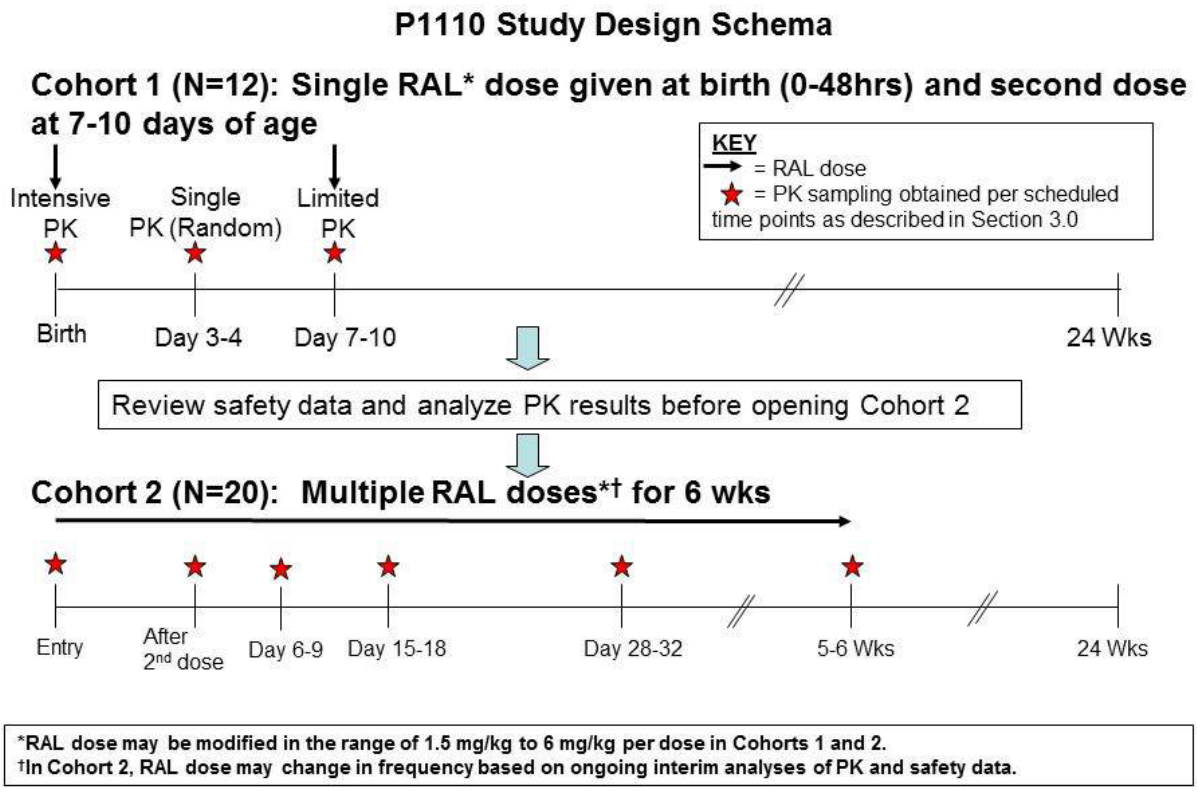
Optional genotyping (Cohorts I and II)

Optional genotyping for UGT1A1 and *SLCO1B1* polymorphisms was performed in infants undergoing PK sampling to determine how polymorphisms such as *UGT1A1 *28/*28* genotype, associated with decreased UGT1A1 activity, impacted raltegravir elimination and biliary elimination of bilirubin in the neonate. UGT1A1 activity is reduced in all neonates at birth but increases rapidly over the first weeks of age. The effect of UGT1A1 polymorphisms on the metabolism of raltegravir during this period is unknown. The potential association of *SLCO1B3* polymorphisms with neonatal hyperbilirubinemia was also examined.

PK sampling

Blood was collected at the time points shown in the revised study schema and as in Figure 1.

Figure 1. P1110 Study Design Schema



Pharmacokinetic sampling for Cohort I included the following:

• Dose 1 (within 48 hours of birth) pre-dose, 1 to 2 h post-dose, 4 to 8 h post-dose, 12 (±1) h post-dose and 24 (±1) h post-dose.

• Day 3 to 4 one random PK sample was obtained with laboratory evaluations on Day 3 to 4

• Dose 2 (7 to 10 days) pre-dose, 1-2 h post-dose and 24 (±1) h post-dose

Pharmacokinetic sampling for Cohort II included the following:

• Within 1 h pre-first dose, then 1 to 2, 6 to 10 and 20 to 24 h post-dose

• After second dose one sample obtained 3 to 6 h post-dose with laboratory evaluations

Then at visits in the following windows:

• Days 6 to 9 within 1 h pre-dose of initiating 3 mg/kg BID
• Days 15 to 18 within 1 h pre-dose, then 1 to 2, 4 to 6 and 8 to 12 h post-dose
• Days 28 to 32 within 1 h pre-dose of initiating 6 mg/kg twice daily
• Weeks 5 and 6 (days 33 to 42) within 1 hour pre-dose and 3 to 6 h post-dose.
PK sampling was ideally scheduled after raltegravir had reached steady state (~ 7 to 10 days after the dose increase).

Plasma samples were analysed for raltegravir concentration by UAB using HPLC-MS/MS. Two validated procedures were used to support this study, one with a linear calibration range of 1 to 3,000 ng/mL and the other with a linear calibration range of 10 to 10,000 ng/mL.

Population PK modelling and simulation were conducted after the completion of Cohort I to generate a multiple dosing scheme for Cohort II. Data were to be integrated from P1110 Cohort I, P1097 and P1066 (Cohorts IV 6 months to <24 months and V 4 weeks to 6 months) to construct a population PK model capable of describing raltegravir PK in neonates. A two-compartment model was fitted using nonlinear mixed effects modelling (NONMEM) version VII software, where various population attributes including, but not limited to, age, weight, sex and creatinine clearance were examined to determine their influence on the PK of raltegravir. Following completion of Cohort II, the population PK model was updated using the PK data collected at all visits in Cohort II.

Sample size

The study was to enroll approximately 50 mother-infant pairs to accrue a minimum of 32 PK-evaluable HIV-1-exposed neonates.

Results

- There were 16 neonates enrolled into Cohort I (10 raltegravir-unexposed and 6 raltegravir-exposed *in utero*). They all completed 2 doses and safety follow up to 24 weeks and 14 were evaluable for PK.
- There were 26 neonates enrolled in Cohort II, all of whom were unexposed to raltegravir *in utero*, of which 23 completed 6 weeks of treatment, 22 completed safety follow up to 24 weeks and 25 were evaluable for PK.

Using the IMPAACT SOP criteria there was one reportable protocol deviation that concerned one neonate in Cohort II who did not receive raltegravir for 4 days following the first 2 doses that were given in the hospital. Treatment resumed at the day 6 to 9 visit.

Based on the MAH's criteria there were 4 major deviations concerning 4 neonates who received an incorrect dose. None of these 4 neonates was excluded from PK analysis and none had AEs during the incorrect dosing period.

In Cohort I, 68.8% of the mothers were Black or African American and 31.3% were Hispanic or Latino with a median age of 24.5 years. In Cohort II, 69.2% of the mothers were Black or African American and 73.1% were Hispanic or Latino with a median age of 27 years. Approximately half of neonates enrolled in both Cohorts were female and 80% were delivered by Caesarean section. The median gestational age at birth was 38-39 weeks and the median birth weight was about 3 kg.

The most commonly reported medical history for the neonates was increased AST (Cohort I 43.8% and Cohort II 15.4%). Two in Cohort I and one in Cohort II had neonatal jaundice.

The most frequently used PMTCT regimens consisted of NNRTI +/- NRTI (56.3% in Cohort I and 96.2% in Cohort II; mostly NVP plus ZDV). Zidovudine was included in all regimens except for 5 neonates (1 in Cohort I, 4 in Cohort II) who received NVP alone.

All 16 in Cohort I received both observed single-doses of raltegravir. Adherence to study drug in Cohort II was good, with 92.3% having 100% adherence, none with < 80% adherence and a median of 41 (range 1-43) days on raltegravir.
The two neonates considered non-evaluable had switched samples or incomplete data due to refusing further blood draws.

PK data from raltegravir-unexposed infants in Cohort I

Three raltegravir-unexposed neonates who received a first dose of 3 mg/kg had AUC_{0-12} values > 28 hr*mg/L (target).

Table 2. Individual Results and Summary Statistics of PK Parameters for the First Dose (3 mg/kg, within 48 hours of birth) Administered to Raltegravir-Unexposed Neonates (N=6*)

Cohort	Sex	Time to First Dose (h)	Weight (kg)	Dose (mg)	Dose (mg/kg)	T1/2 (hr)	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)	V/F (L)	CL/F (L/hr)	AUC_{12} (hr*mg/L)	AUC_{24} (hr*mg/L)	AUC_{inf} (hr*mg/L)
I	PPD	25.3	PPD	10.0	PPD	7.88	6.90	5317.70	50.53	131.50	1.09	0.10	46.28	79.56	103.89
I		24.5		10.0		12.75	6.38	3199.70	71.23	120.80	1.77	0.10	34.31	62.33	103.92
I		25.4		8.0		9.90	4.25	2702.40	73.00	21.20	2.08	0.15	24.85	37.89	54.87
I		12.5		10.0		11.27	4.08	4286.50	68.08	105.60	1.54	0.09	39.98	65.48	105.66
I		9.9		12.0		15.69	4.17	2002.60	143.00	5.00	2.99	0.13	18.89	33.67	90.74
I		13.6		10.0		15.49	24.00	3651.30	68.42	500.10	1.38	0.06	22.03	59.05	162.43
n		6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
avg		18.51	3.07	10.00	3.26	12.16	8.30	3526.70	79.04	147.37	1.81	0.10	31.06	56.33	103.59
sd		7.27	0.36	1.26	0.20	3.10	7.79	1175.57	32.35	180.73	0.67	0.03	10.86	17.44	34.65
cv		39.27	11.63	12.65	6.13	25.50	93.89	33.33	40.93	122.64	37.08	28.88	34.98	30.96	33.45
median		19.06	PPD	10.00	PPD	12.01	5.32	3425.50	69.83	113.20	1.65	0.10	29.58	60.69	103.90
min		9.88		8.00		7.88	4.08	2002.60	50.53	5.00	1.09	0.06	18.89	33.67	54.87
max		25.35		12.00		15.69	24.00	5317.70	143.00	500.10	2.99	0.15	46.28	79.56	162.43
gm		17.24	3.05	9.93	3.25	11.82	6.51	3360.89	74.79	66.81	1.72	0.10	29.48	53.88	98.67

*Footnotes:

Clast = Concentration at Tlast, representing Ctrough

One suject - no Day 3 to 4 sample was collected, thus T1/2 and CL/F could not be reasonably calculated. The Ke from 24.25 to 143 hrs was calculated by using 1/2 BLQ (5 ng/mL) at 143 hours instead of 0 ng/mL.

One subject, was one of the first 6 RAL-unexposed neonates enrolled into Cohort I but was subsequently determined not PK evaluable by the protocol team, and therefore data not included in this table.

One subject, was not one of the first 6 enrolled RAL-unexposed neonates; however this patient received a first dose of 3 mg/kg rather than 2 mg/kg in error and therefore is included in this table

Table 3. Individual Results and Summary Statistics of PK Parameters for the First Dose (2 mg/kg, within 48 hours of birth) Administered to Raltegravir-Unexposed Neonates (N = 3)

Cohort	Sex	Time to First Dose (h)	Weight (kg)	Dose (mg)	Dose (mg/kg)	T1/2 (hr)	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)	V/F (L)	CL/F (L/hr)	AUC_{12} (hr*mg/L)	AUC_{24} (hr*mg/L)	AUC_{inf} (hr*mg/L)
I	PPD	33.1	PPD	8.4	PPD	32.82	4.35	4099.60	28.77	1220.00	3.60	0.08	28.95	46.76	110.43
I		24.9		5.0		24.25	4.28	4323.40	28.52	2439.10	0.98	0.03	44.00	81.98	178.45
I		24.2		6.0		6.34	4.65	2227.80	28.40	117.50	2.26	0.25	17.44	22.61	24.33
n		3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
avg		27.41	3.06	6.47	2.14	21.14	4.43	3550.27	28.56	1258.87	2.28	0.12	30.13	50.45	104.40
sd		4.95	1.01	1.75	0.12	13.51	0.20	1150.74	0.19	1161.29	1.31	0.11	13.32	29.85	77.24
cv		18.07	32.86	27.02	5.78	63.92	4.44	32.41	0.66	92.25	57.51	98.28	44.20	59.17	73.98
median		24.90	PPD	6.00	PPD	24.25	4.35	4099.60	28.52	1220.00	2.26	0.08	28.95	46.76	110.43
min		24.22		5.00		6.34	4.28	2227.80	28.40	117.50	0.98	0.03	17.44	22.61	24.33
max		33.12		8.40		32.82	4.65	4323.40	28.77	2439.10	3.60	0.25	44.00	81.98	178.45
gm		27.13	2.96	6.32	2.14	17.15	4.42	3405.24	28.56	704.49	2.00	0.08	28.11	44.26	78.26

Clast = Concentration at Tlast, representing Ctrough

After lowering the first dose to 2 mg/kg two neonates exceeded the AUC targets and one of these had values that were double the targets.

Interim POPPK model

An "Interim Population PK Model" was developed using 6 raltegravir-unexposed Cohort 1 neonates, enriched by data from 24 HIV-1-infected infants in P022 aged 4 weeks to 2 years. The Interim Population PK Model involved 2-compartment linear disposition, first-order oral absorption and body-weight based allometric correction of clearances and volumes with fixed exponents of 0.75 and 1.0, respectively. It also included empirical hyperbolic functions for the increases in clearance and rate constant of absorption with age. No additional covariate effects were included in this model.

The model was used to perform simulations to select a 6-week dose regimen for raltegravir-unexposed neonates in Cohort II. Ten dose regimen options (Table 4) were simulated to identify the most appropriate regimen.

Table 4. Dosing Regimens Simulated to Guide Dose Selection in P080 Cohort II

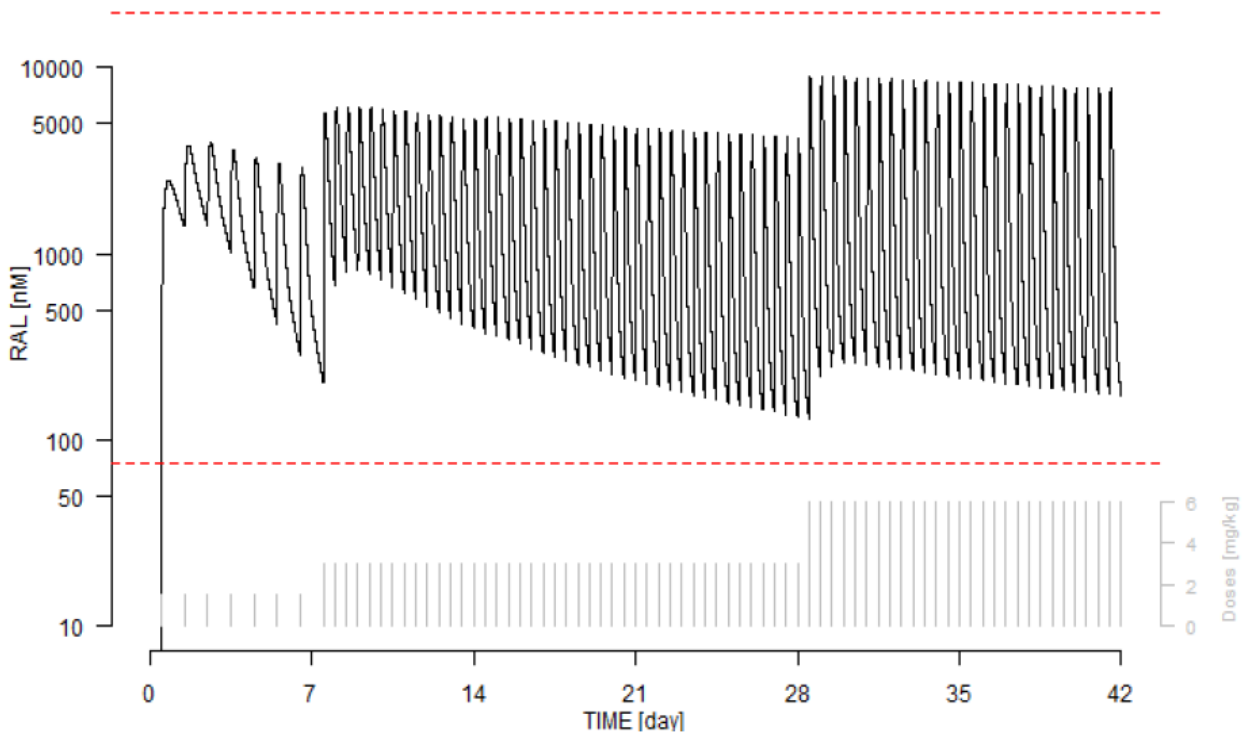
	Days 1-7	**Days 8-14**	**Days 15-21**	**Days 22-28**	**Days 29-35**	**Days 36-42**
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Regimen No	BW change: 3.0 – 3.2 kg	BW change: 3.2-3.3 kg	BW change: 3.3-3.7kg		BW change: 3.7-4.0 kg	
1	2 mg/kg QD	3 mg/kg BID				
2	3 mg/kg QD	3 mg/kg BID			4 mg/kg BID	
3	2 mg/kg QD	2 mg/kg BID			6 mg/kg BID	
4	2 mg/kg QD	2 mg/kg BID	6 mg/kg BID			
5	3 mg/kg QD		3 mg/kg BID		6 mg/kg BID	
6	2 mg/kg QD	4 mg/kg QD	6 mg/kg BID			
7	2 mg/kg QD	3 mg/kg BID			6 mg/kg BID	
8	2 mg/kg QD	6 mg/kg QD			6 mg/kg BID	
9	3 mg/kg QD	3 mg/kg BID			6 mg/kg BID	
10	1.5 mg/kg QD	3 mg/kg BID			6 mg/kg BID	

Abbreviations: BID: twice-daily; BW: body weight; QD: once-daily;

Note: BW change calculated using BW = 3 + 9.289*(1 – exp(0.983*AGE)), AGE expressed in years. This empirical equation was obtained by fitting the actual BW data

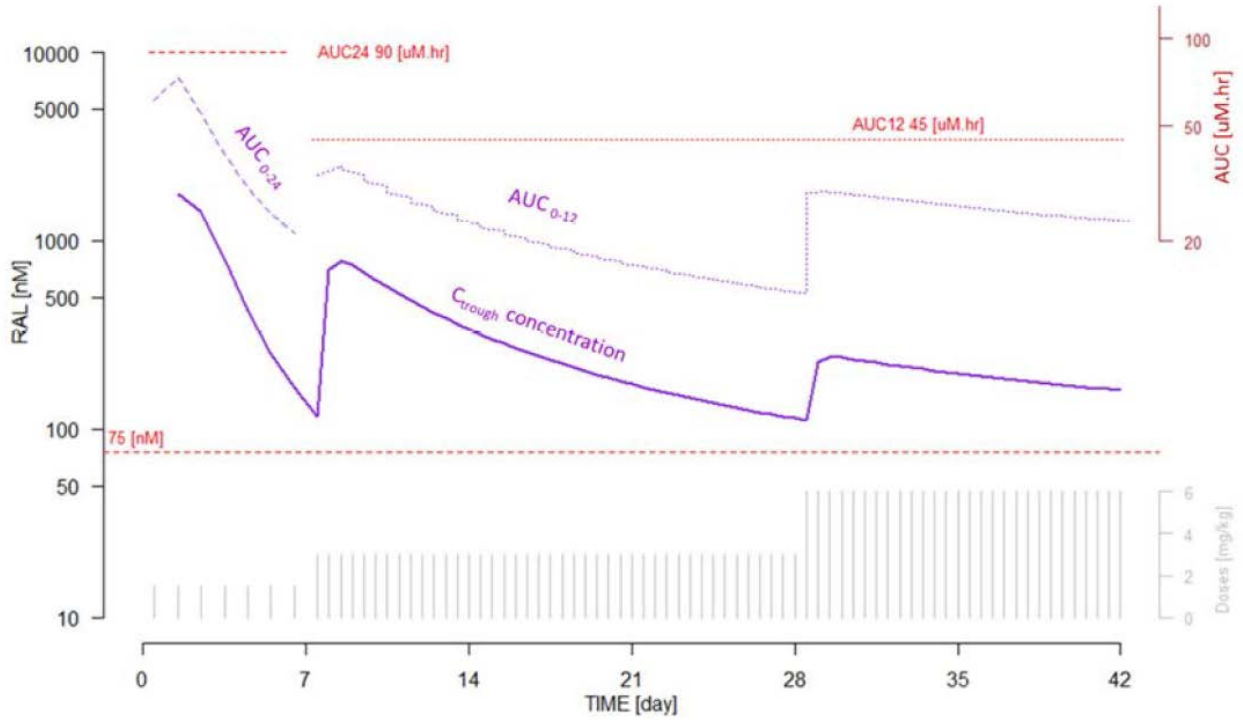
Simulations included 10 candidate dose regimens adhering to the predefined PK targets of C_{trough} >33.3 ng/mL (75 nM), Cmax <8720 ng/mL (19.63 µM), AUC_{0-24} <40 hr*mg/L (90 µM*hr) and AUC_{0-12} <20 hr*mg/L (45 µM*hr) for a typical neonate. The selected regimen was 1.5 mg/kg QD from birth through day 7 followed by 3 mg/kg BID during days 8 through 28 and the approved dose (6 mg/kg BID) thereafter.

Figure 2. Simulated Concentration-Time Profile of Raltegravir in a Typical Raltegravir-Unexposed Neonate at the Proposed Dosing Regimen (semi-log scale)



Note: the dashed horizontal lines at 75 nM and 19.63 µM are the Cmin and Cmax targets, respectively.

Figure 3. Simulated Daily AUC and Ctrough Values for a Typical Individual Receiving the 6-week Dosing Regimen Recommended; Ctrough, AUC0-24 and AUC0-12 Targets are Met



Simulation results of the ten dose regimens are shown in Table 5. Colour (and symbol) coding was added to emphasize if PK targets are always met with large margins (in green or √), met with smaller margins (in yellow or ~) and not met (in red or X).

Table 5. Attainment of PK endpoints simulated from the interim population PK model

Regimen No.*	C_{min} > 75 nM	C_{max} < 19.63 µM	AUC_{0-24} < 90 µM.hr (QD)	AUC_{0-12} < 45 µM.hr (BID)
1	0% (42) X	-69% (9) ✓	-10% (2) ✓	-25% (8) ✓
2	+54% (42) ✓	-60% (3) ✓	+35% (2) X	-23% (8) ✓
3	+10% (29) ~	-54% (29) ✓	-10% (2) ✓	-39% (30) ✓
4	+110% (42) ✓	-47% (15) ✓	-10% (2) ✓	-6% (15) ~
5	+39% (15) ✓	-54% (29) ✓	+35% (2) X	-39% (29) ✓
6	+96% (15) ✓	-47% (15) ✓	-10% (2) ✓	-6% (15) ~
7	+65% (29) ✓	-54% (29) ✓	-10% (2) ✓	-25% (8) ✓
8	-7% (29) X	-42% (9) ✓	-10% (2) ✓	-39% (30) ✓
9	+65% (29) ✓	-54% (29) ✓	+35% (2) X	-23% (8) ✓
10	+65% (29) ✓	-54% (29) ✓	-33% (2) ✓	-25% (8) ✓

*Regimens described in Table 4.

Abbreviations: AUC0-12: area under the concentration-time curve from time 0 to 12 hours after dose;

AUC0-24: area under the concentration-time curve from time 0 to 24 hours after dose; BID: twice daily;

Cmax: maximum concentration; Cmin: minimum concentration; QD: once daily; ticks designate PK endpoints that were met.

Note: Results are expressed as Closest Percentage of Endpoint (Day of Occurrence)

In all ten scenarios, the Cmax criterion is always met while all but two did not meet the C_{min} criterion.

Regimens 3, 4, 6, 7 and 10 met all PK endpoint criteria but regimens 4 and 6 were considered too close (up to 94%) to the AUC_{0-12} maximum thus were not retained for consideration.

Regimens 7 and 10 were better than regimen 3 in exceeding the C_{min} endpoint, and regimen 10 appeared superior to regimen 7 for AUC_{0-24} in the QD period, as it gave the lowest predicted value that did not exceed 67% of the pre-specified AUC target. This is consistent with the fact that regimen 10 contained the lowest proposed dose (1.5 mg/kg) during the first week of life. Regimen 10 was considered better than 7 for patient adherence with absolute dosing value simply doubling between each change.

Ultimately, regimen 10 was recommended for Cohort II for P080. This regimen consisted of 1.5 mg/kg QD in Week 1, 3.0 mg/kg BID in Weeks 2 to 4 of age and 6.0 mg/kg BID in Weeks 5 and 6.

PK data from Cohort II

The selected dosing regimen (see above) was assessed in the first 8 neonates (interim analysis population) to confirm if the observed PK parameters were as expected from the simulations and within the specified PK targets.

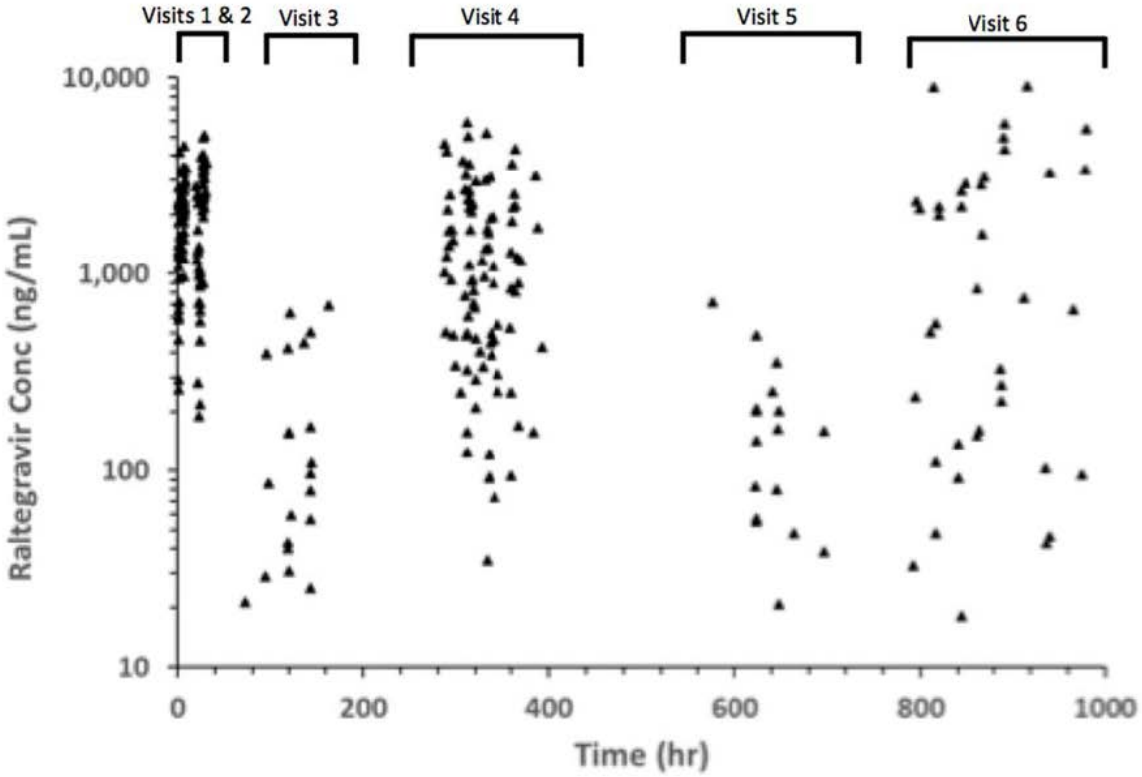
The geometric mean PK parameters from the first 8 raltegravir-unexposed neonates met the pre-specified PK targets except for a slightly higher mean AUC_{0-24} after the first dose at 1.5 mg/kg QD. Enrolment proceeded without any dose adjustments. The GM for all 25 raltegravir-unexposed neonates achieved the pre-specified PK targets after the first dose of 1.5 mg/kg QD and during 3 mg/kg BID on day 15 to 18.

Individual values did not always meet the pre-specified AUC targets. As shown in the figure below there was considerable scatter of values and the tables that follow show that:

- AUC_{0-24} frequently exceeded 40 hr*mg/L (90 µM*hr)

- AUC_{0-12} frequently exceeded 20 hr*mg/L (45 µM*hr)

Figure 4. Individual raltegravir concentration: Time profiles of all Raltegravir Unexposed neonates in Cohort II (N=25)



Cohort II: PK Visit 1 (1.5 mg/kg QD), PK Visit 2 (1.5 mg/kg QD), PK Visit 3 (3.0 mg/kg BID), PK Visit 4 (3.0 mg/kg BID), PK Visit 5 (6.0 mg/kg BID), PK Visit 6 (6.0 mg/kg BID)*

Table 6. Individual Results and Summary Statistics of PK Parameters for All Raltegravir-Unexposed Neonates After First Dose (1.5 mg/kg QD, within 48 hours of birth) in Cohort II, N = 25*

Cohort	Sex	Time to First Dose (h)	Weight (kg)	Dose (mg)	Dose (mg/kg)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	T_{last} (hr)	C_{last} (ng/mL)	AUC_{all} (hr*mg/L)	V_z/F (L)	CL/F (L/hr)	AUC_{24} (hr*mg/L)
II	PPD	42.00	PPD	4.0	PPD	6.14	1.72	1421.40	22.45	191.10	18.33	1.77	0.20	18.60
II		37.67		4.0		36.02	6.00	2256.80	21.62	1670.90	39.84	1.64	0.03	43.73
II		47.45		5.0		7.84	6.18	2693.30	23.68	573.20	38.75	1.25	0.11	38.93
II		22.52		4.6		16.68	6.92	2102.10	24.42	1015.90	37.22	1.80	0.07	36.79
II		22.38		5.0		32.34	9.03	3466.40	19.17	2789.20	55.65	1.26	0.03	68.45
II		25.98		5.0			20.88	2492.60	20.88	2492.60	39.97			
II		19.85		5.0		18.32	6.55	1629.30	23.38	862.00	29.93	2.51	0.09	30.46
II		24.48		5.0		12.54	7.20	2835.10	21.53	1284.10	44.62	1.33	0.07	47.58
II		36.53		5.0		12.45	6.43	2323.30	23.47	899.60	39.15	1.62	0.09	39.62
II		20.68		5.0		58.29	7.23	3031.80	21.93	2545.60	52.12	1.26	0.02	57.32
II		43.60		5.0		12.45	6.47	2658.40	23.42	1034.70	41.08	1.51	0.08	41.67
II		4.45		5.0		233.98	6.33	2408.90	21.33	2304.20	43.14	2.06	0.01	49.27
II		16.58		6.0		9.82	1.67	4162.40	23.13	977.00	54.81	1.24	0.09	55.64
II		24.45		5.0		18.18	6.35	4507.60	23.52	2341.90	77.22	0.95	0.04	78.33
II		37.55		5.0		9.69	6.88	2222.30	22.65	719.50	33.75	1.60	0.11	34.68
II		36.70		6.0		5.53	6.77	1838.70	21.82	279.20	23.07	1.89	0.24	23.60
II		40.57		4.0		39.61	6.68	1505.10	20.75	1176.60	25.87	2.46	0.04	29.59
II		40.52		4.0		10.19	6.00	1524.70	23.75	455.60	22.26	2.03	0.14	22.38
II		33.58		4.0		6.68	6.00	1333.20	23.42	219.00	18.68	1.86	0.19	18.80
II		40.00		5.0		30.53	1.00	1286.40	23.55	651.50	20.53	4.47	0.10	20.82
II		38.20		6.0		12.98	6.12	3311.90	22.63	1371.30	54.88	1.39	0.07	56.69
II		281.40		5.0		9.42	1.50	2410.10	23.08	709.60	38.27	1.42	0.10	38.90
II		43.33		5.0		11.43	6.08	2037.30	23.58	704.80	31.01	1.93	0.12	31.30
II		36.42		5.0		9.91	6.00	3517.50	23.08	1065.40	54.93	1.02	0.07	55.88
II		36.23		5.0		11.56	6.03	3347.90	21.70	1308.00	45.63	1.24	0.07	48.44
n		25	25	25	25	24	25	25	25	25	25	24	24	24
avg		42.13	2.87	4.90	1.71	26.36	6.32	2492.98	22.56	1185.70	39.23	1.73	0.09	41.14
sd		50.92	0.34	0.57	0.13	46.07	3.63	872.93	1.22	761.62	14.18	0.71	0.06	15.78
cv		120.89	11.86	11.72	7.47	174.79	57.49	35.02	5.40	64.23	36.16	41.22	62.39	38.35
median		36.53	PPD	5.00	PPD	12.45	6.33	2408.90	23.08	1015.90	39.15	1.61	0.09	39.27
min		4.45		4.00		5.53	1.00	1286.40	19.17	191.10	18.33	0.95	0.01	18.60
max		281.40		6.00		233.98	20.88	4507.60	24.42	2789.20	77.22	4.47	0.24	78.33
gm		32.29	2.85	4.87	1.71	15.79	5.37	2349.91	22.52	947.90	36.74	1.63	0.07	38.20

Clast = Concentration at Tlast, representing Ctrough

In one subject- Cannot calculate all PK parameters (elimination rate constant) for the first dose at 1.5 mg/kg because the concentration increased relative to previous one (20 to 28 hours at entry visit intensive PK)

Table 7. Individual Results and Summary Statistics of PK Parameters for the All Raltegravir-Unexposed Neonates After 3.0 mg/kg BID Dose (Day 15 to 18) in Cohort II, N = 24*

Cohort	Sex	Weight (kg)	Dose (mg)	Dose (mg/kg)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	T_{last} (hr)	C_{last} (ng/mL)	AUC_{all} (hr*mg/L)	V_z/F (L)	CL_{ss}/F (L/hr)	AUC_{12} (hr*mg/L)	Est C12h (ng/mL)
II	PPD	PPD	9.0	PPD	1.45	1.00	1352.20	8.00	73.60	4.61	3.97	1.90	4.74	10.89
II			10.0		1.86	4.08	2082.90	8.08	470.10	9.65	2.53	0.94	10.62	109.31
II			10.0		1.57	4.63	1675.70	8.22	343.80	9.58	2.22	0.98	10.21	64.86
II			10.0		1.75	1.05	3651.40	8.00	170.30	10.62	2.31	0.91	10.96	34.98
II			10.0		1.91	4.42	1696.20	8.10	445.00	8.94	2.79	1.01	9.87	107.77
II			10.0		2.80	1.52	3795.20	8.07	1111.30	19.52	1.81	0.45	22.31	420.15
II			10.0		2.25	1.25	5020.90	8.17	673.50	20.07	1.51	0.46	21.59	207.49
II			10.0		2.31	1.58	5239.70	9.95	460.90	23.78	1.36	0.41	24.49	249.36
II			10.0		3.69	4.83	2560.60	8.85	1203.10	15.34	2.92	0.55	18.20	665.66
II			8.0		3.81	1.70	3201.50	9.38	825.60	17.48	2.29	0.42	19.20	512.72
II			8.0		3.32	4.00	4339.50	10.28	1170.30	27.09	1.33	0.28	28.78	817.37
II			8.0		4.18	5.08	3012.00	8.83	1618.30	16.67	2.34	0.39	20.66	957.18
II			12.0		4.09	4.55	1097.00	8.58	553.80	5.94	9.60	1.63	7.37	310.05
II			8.0		2.00	1.83	3157.30	8.35	425.10	13.41	1.61	0.56	14.30	120.00
II			10.0		1.50	4.38	1955.10	8.37	309.80	8.63	2.36	1.09	9.17	57.97
II			10.0		2.35	1.75	3653.10	8.45	290.50	12.05	2.67	0.79	12.69	101.92
II			8.0		3.58	1.38	4222.60	8.20	1478.40	22.84	1.54	0.30	26.82	708.73
II			8.0		2.26	4.00	1649.50	8.00	484.10	9.43	2.47	0.76	10.55	142.08
II			8.0		2.19	1.00	3140.80	8.00	253.40	10.00	2.38	0.76	10.58	71.26
II			10.0		3.03	4.05	2238.70	8.05	897.00	13.36	2.79	0.64	15.69	363.54
II			10.0		1.91	1.15	2661.10	8.23	211.40	9.31	2.83	1.03	9.74	53.94
II			8.0			8.48	2965.70	8.48	2965.70	20.49				
II			10.0		2.28	1.00	5953.10	8.00	704.20	21.85	1.40	0.43	23.49	209.24
II			10.0		3.39	1.17	4612.80	8.00	932.30	18.31	2.34	0.48	20.86	411.23
n		24	24	24	23	24	24	24	24	24	23	23	23	23
avg		3.18	9.38	2.95	2.59	2.91	3122.28	8.44	752.98	14.54	2.58	0.75	15.78	291.64
sd		0.32	1.10	0.27	0.87	1.95	1308.11	0.62	630.55	6.15	1.65	0.41	6.82	273.42
cv		10.16	11.69	8.99	33.49	67.12	41.90	7.34	83.74	42.30	64.02	54.98	43.25	93.75
median		PPD	10.00	PPD	2.28	1.79	3076.40	8.21	518.95	13.39	2.34	0.64	14.30	207.49
min			8.00		1.45	1.00	1097.00	8.00	73.60	4.61	1.33	0.28	4.74	10.89
max			12.00		4.18	8.48	5953.10	10.28	2965.70	27.09	9.60	1.90	28.78	957.18
gm		3.16	9.31	2.94	2.45	2.34	2849.48	8.42	557.99	13.23	2.32	0.66	14.30	176.11

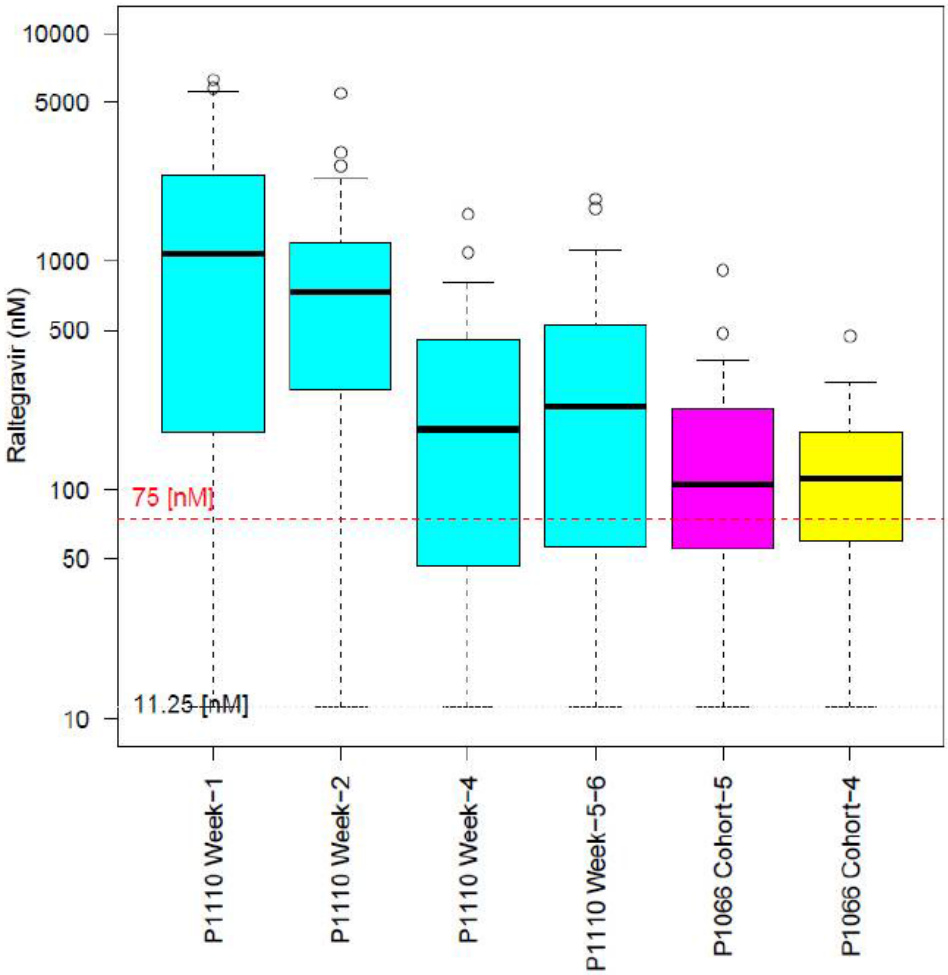
Est C12hr= estimated concentration at 12-hour extrapolated from the individual profile.

One subject- Mother withdrew consent after the first PK visit at 1.5 mg/kg; no 3 mg/kg PK data available.

One subject- Cannot calculate all PK parameters (elimination rate constant) for the 3 mg/kg dose because the concentration at the last time point increased. Infant discontinued RAL after week 4 to 5 visit (hospitalized for weight loss)

The CSR for P080 states that the distribution of observed concentration values in neonates in Cohort II who received the approved dose from 4 weeks of age and infants who received this same dose in P1066 Cohorts IV and V overlapped as shown in Figure 5. However, this figure also shows that the regimen used from birth resulted in considerably greater exposures at least in the first 2 weeks of life compared to those achieved with the regimen used from 4 weeks onwards.

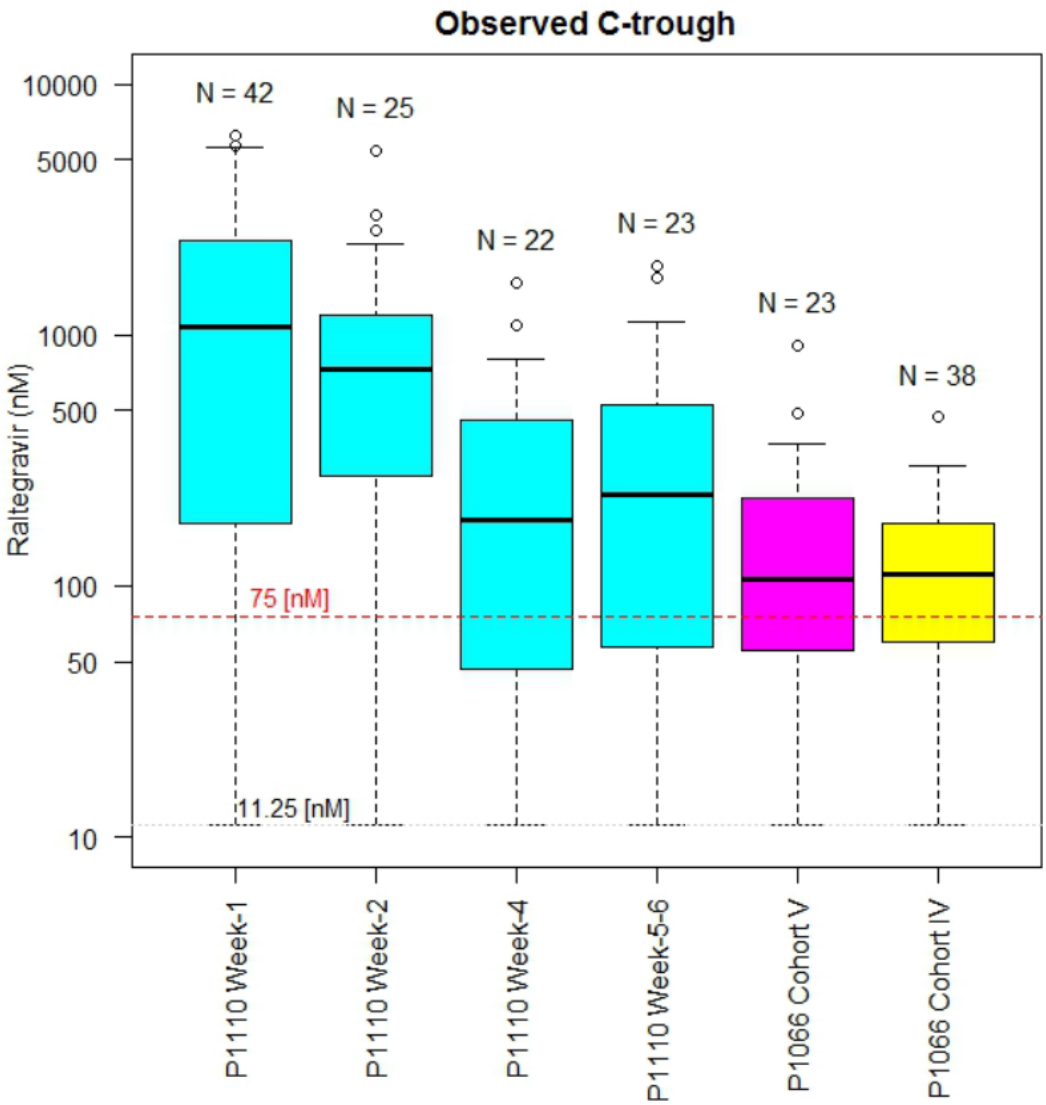
Figure 5. Comparison of Distribution of Raltegravir Concentration Values in Infants ≥ 4 Weeks of Age Receiving 6.0 mg/kg BID in P1110 and P1066



The POPPK report (04mhp6) includes a very similar figure that compares the observed C_{trough} values and shows the same pattern (see below). This report comments that the median trough level went down from 2330 nM (1035 ng/mL) after the first dose on Day 1 to 156 nM (69.3 ng/mL) after one week of 1.5 mg/kg QD dosing in Cohort II due to increased clearance of raltegravir.

With institution of 3 mg/kg BID for the following period from 2 to 4 weeks, the median trough levels decreased from 734 nM (326 ng/mL) in Week 2 to 184 nM (82 ng/mL) in Week 4 as the result of further maturation of the UGT-1A1 enzyme complex. After institution of 6 mg/kg BID at Week 4, the median trough level obtained in Week 5-6 was 233 nM (104 ng/mL). For cohorts IV and V of P022 dosed with 6 mg/kg BID, the median trough was 106 nM (47.1 ng/mL).

Figure 6. Boxplots of observed trough samples in studies MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066



The percentages of neonates and infants who experienced plasma trough raltegravir below 75 nM (33.3 ng/mL) after Week 1, Week 4 and Weeks 5-6 in Cohort II of P1110 and in Cohorts IV and V of P022 varied from 26% to 44%.

The predicted trough concentrations in the two studies gave similar results to the observed values. The median trough after one week was slightly over-predicted by the model.

The observed AUC_{0-24} values exceeded 90 µM.hr (40 µg.hr/mL) in 5/10 (50%) raltegravir-unexposed neonates after the first dose administration on Day 1 compared to 9% of the adult population in P292. After about one week of the 3 mg/kg BID dose at Day 14, 3/9 had AUC_{0-12} >45 µM.hr (20 µg.hr/mL) compared to 0% and 9% of Cohorts IV and V in P022.

Table 8. Summary Observed Trough Concentrations [nM] in studies MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066

	Merck P080/IMPAACT P1110 Cohort II					Merck P022/IMPAACT P1066	
Metric	**Day 2**	**Week 1**	**Week 2**	**Week 4**	**Week 5-6**	**Cohort V**	**Cohort IV**
Minimum*	430	11.3	11.3	11.3	11.3	11.3	11.3
25% Percentile	1590	79.3	274	56.7	56.8	55.1	59.7
Median	2330	156	734	184	233	106	112
75% Percentile	3420	298	1200	455	524	225	177
Maximum	6280	1140	5430	1620	1890	911	471
Underexposed (trough < 75 nM, %)	0	26.3	8	27.3	30.4	43.5	34.2
Mean Time-since-last-dose (hr)	22.5	24.1	12.1	12.4	13.3	11.5	12.2
Mean Age (weeks)	0.329	0.944	2.13	3.98	5.34	23.6	65.2

Figure 7. Boxplots of AUC levels Derived from Observed Concentrations in Studies MSD P292, MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066

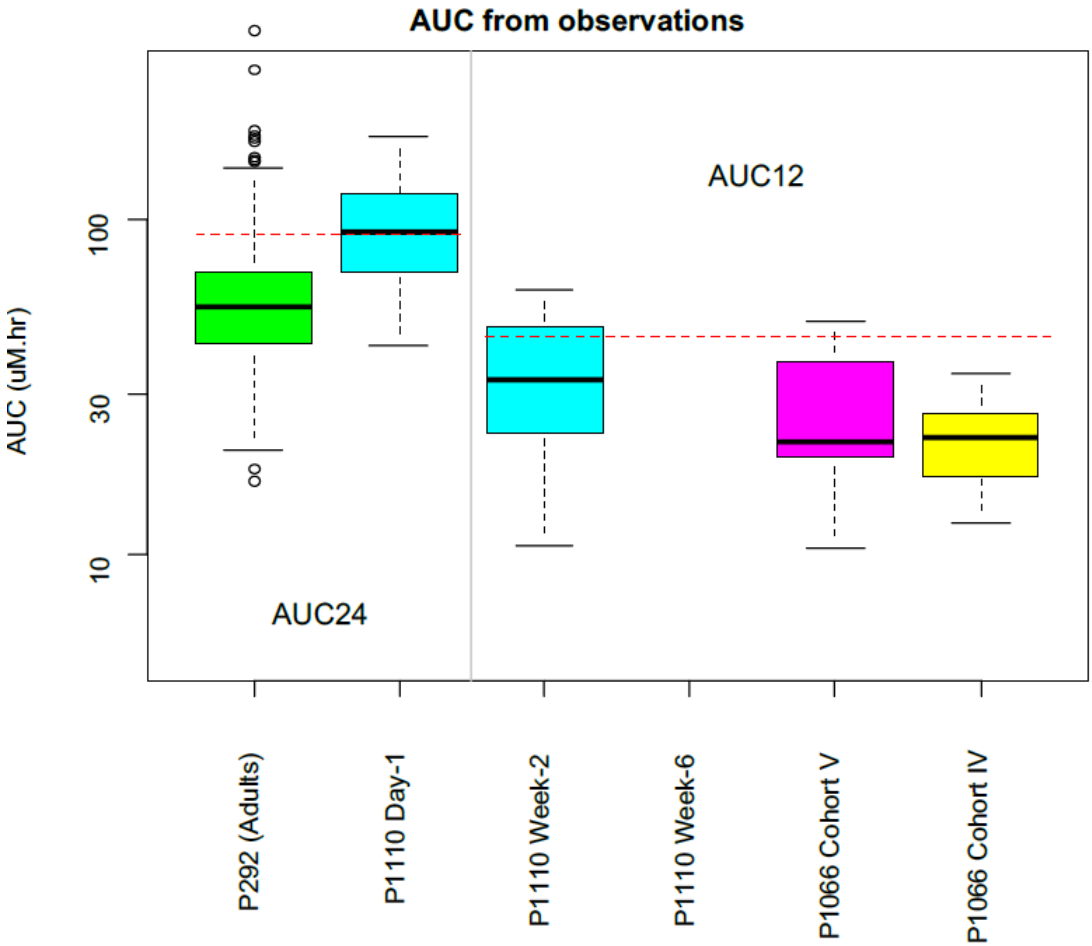


Table 9. Summary AUC levels [µM.hr] Derived from Observed Concentrations in Studies MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066

	AUC_{0-24}		AUC_{0-12}		
	Merck P292 (Adults)	Merck P080/IMPAACT P1110 Cohort II Day-1	Merck P080/IMPAACT P1110 Cohort II Week-2	Merck P022/IMPAACT P1066	
				Cohort V	Cohort IV
Minimum AUC	16.5	41.7	10.7	10.4	12.4
25% Percentile	42.3	70	23	19.6	17.4
Median	54.6	91.4	33.1	21.7	22.4
75% Percentile	69	114	47.6	37.6	25.9
Maximum AUC	363	176	61.5	50	34.7
Overexposure (%) AUC_{0-24}: > 90000 µM.hr AUC_{0-12}: > 45000 µM.hr	9	50	33	9	0

Due to insufficient observed data to determine AUC_{0-12} for neonates during 5-6 weeks, model predicted values were used to compare exposures using 6 mg/kg BID with those in Cohorts IV and V in P022. The criterion of 45 µM.hr (20 µg.hr/mL) was predicted to be exceeded by 41% of neonates during Week 5-6.

Figure 8. Boxplots of Predicted AUC Levels in Studies MSD P292, MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066

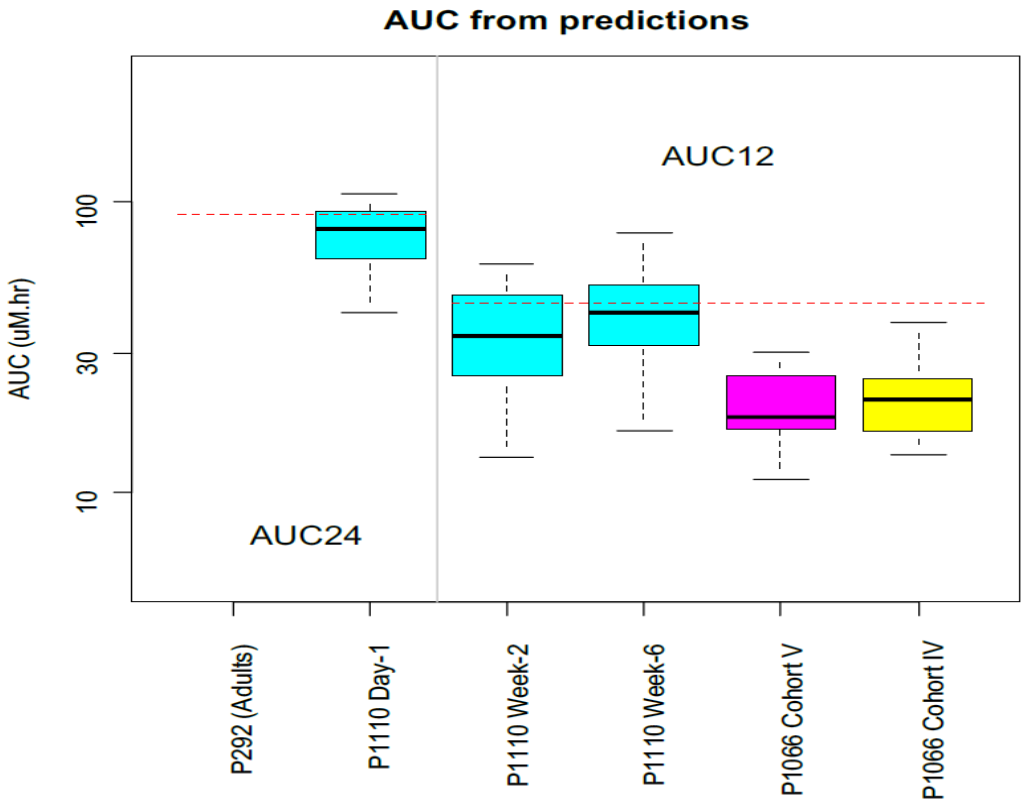


Table 10. Summary Predicted AUC Levels [µM.hr] in Studies MSD P080/IMPAACT P1110 and MSD P022/IMPAACT P1066

	AUC_{0-24}	AUC_{0-12}			
	Merck P080/IMPAACT P1110 Cohort II Day-1	Merck P080/IMPAACT P1110		Merck P022/IMPAACT P1066	
		Cohort II Week 2	Cohort II 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}: > 90000 µM.hr AUC_{0-12}: > 45000 µM.hr	33.3	29.2	41.2	0	0

PK data from raltegravir-exposed infants in Cohort I

Because of the efficient transplacental transfer of raltegravir 1.5 mg/day was selected as the initial dose for the raltegravir-exposed neonates in Cohort I. Four of 6 raltegravir-exposed neonates exceeded the AUC_{0-12} <28 hr*mg/L target. All six met the Cmax < 8720 ng/mL target.

Table 11. Individual results and summary statistics of PK parameters for all raltegravir exposed neonates after first dose of 1.5 mg/kg (within 48 hours of birth) in Cohort I (N=6)

	Cohort	Sex	Time From Birth to First Dose (h)	Time from Mom Dose to Delivery (h)	Weight (kg)	Dose (mg)	Dose (mg/kg)	T1/2 (hr)	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)	V/F (L)	CL/F (L/hr)	AUC_{12} (hr*mg/L)	AUC_{24} (hr*mg/L)	AUC_{inf} (hr*mg/L)
	I	PPD	22.8	9.0	PPD	4.5	PPD	9.25	11.00	1015.40	74.77	15.10	1.69	0.13	7.95	17.92	35.50
	I		40.5	12.0		4.0		18.61	13.25	3342.10	65.00	603.90	0.69	0.03	33.53	70.69	156.62
	I		44.9	11.4		6.0		6.04	1.75	881.10	42.17	12.50	4.46	0.51	7.78	10.79	11.71
	I		38.8	8.4		5.0		11.74	5.00	3562.90	48.92	349.90	0.93	0.05	34.66	62.04	91.06
	I		38.2	10.0		5.0		19.17	4.00	2905.40	30.97	1254.10	1.38	0.05	29.28	54.96	100.04
	I		39.5	19.1		4.0		17.12	4.00	3552.80	30.00	1342.20	0.98	0.04	33.48	58.85	100.55
n			6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
avg			37.45	11.67	2.84	4.75	1.68	13.65	6.50	2543.28	48.64	596.28	1.69	0.13	24.45	45.87	82.58
sd			7.56	3.90	0.46	0.76	0.12	5.44	4.54	1258.99	18.18	587.95	1.41	0.19	12.97	25.06	51.81
cv			20.19	33.44	16.14	15.96	7.31	39.86	69.87	49.50	37.37	98.60	83.20	139.57	53.06	54.63	62.74
median			39.17	10.72	PPD	4.75	PPD	14.43	4.50	3123.75	45.55	476.90	1.18	0.05	31.38	56.90	95.55
min			22.80	8.45		4.00		6.04	1.75	881.10	30.00	12.50	0.69	0.03	7.78	10.79	11.71
max			44.90	19.12		6.00		19.17	13.25	3562.90	74.77	1342.20	4.46	0.51	34.66	70.69	156.62
gm			36.66	11.22	2.81	4.70	1.67	12.60	5.23	2188.82	45.87	201.60	1.37	0.08	20.33	37.42	62.50

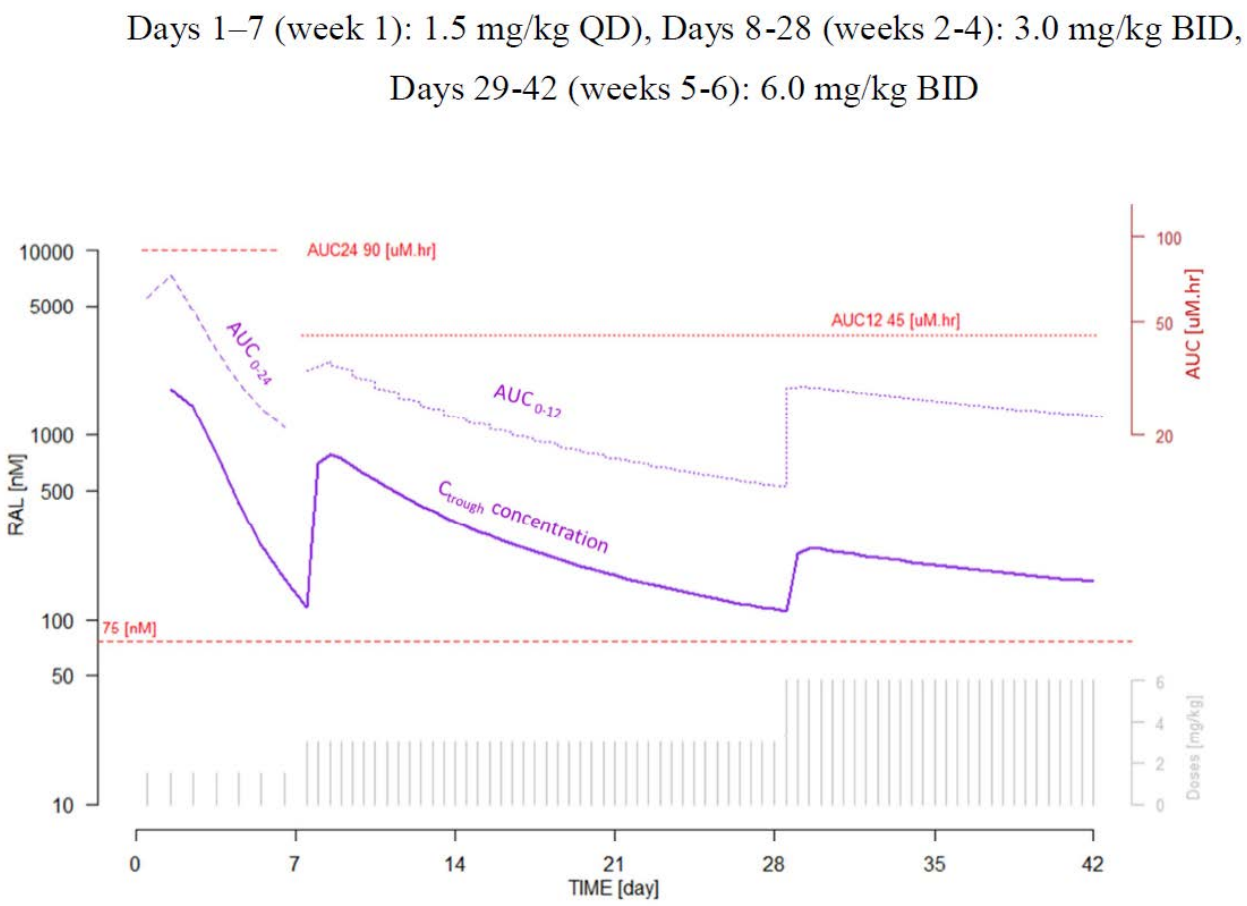
Integrated POPPK model

An "Integrated Population PK Model" was developed that included data from raltegravir-unexposed neonates from Cohorts I and II, raltegravir-exposed neonates from Cohort I, infants in P1066 Cohorts IV and V and 19 mothers from P1097. The total dataset included 65 neonates or infants and 19 mothers.

To support a dosing recommendation over the first 6 weeks of age for raltegravir-exposed neonates, an integrated mother-neonate model was developed, which consisted of two parts: one related to raltegravir PK in the mother and one related to the foetus (later neonate). The fitted PK for the mother compared reasonably well against reported summary PK data of pregnant women in their third trimester while the neonate model was assumed identical for raltegravir-unexposed and raltegravir-exposed neonates. The only difference was that the raltegravir concentration in the central compartment at birth was determined by prior history of exposure in utero instead of being set to zero.

Simulations were conducted assuming a first dose of raltegravir was given at various times postpartum. Using the same predefined PK targets, the final recommendation was made that a raltegravir-exposed neonate should receive the first dose between 24 and 48 hours postpartum so that the trough is predicted to remain above 33 ng/mL and AUC0-24 is predicted to stay below 40 mg*hr/mL.

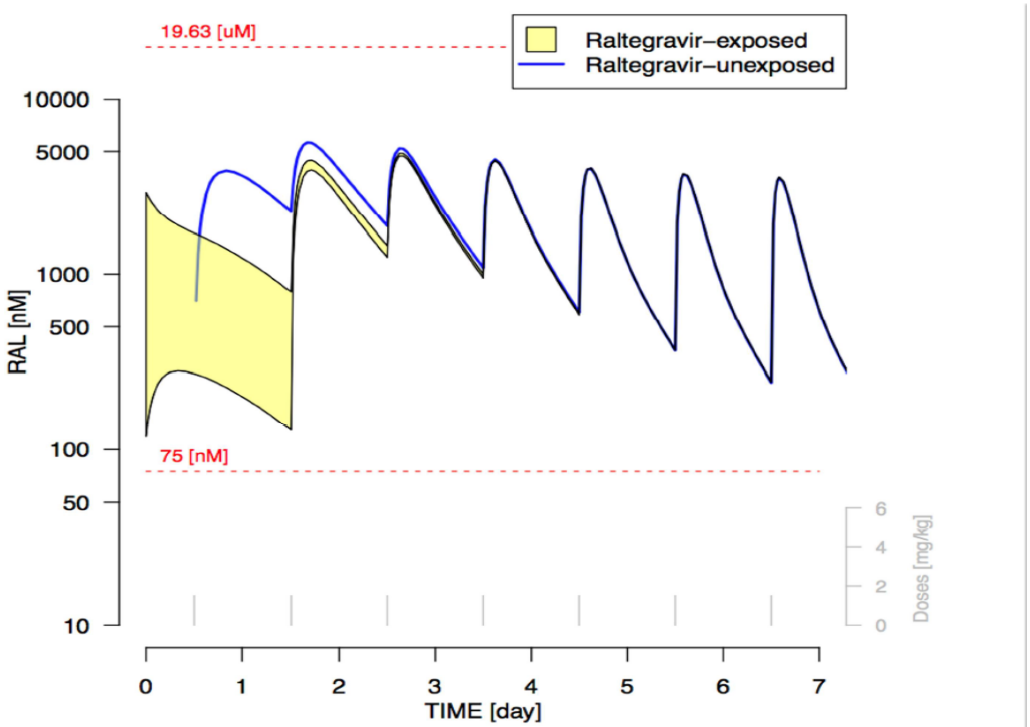
Figure 9. Simulated Daily AUC and Ctrough Values for a Typical Individual Receiving the 6-week Dosing Regimen Recommended; Ctrough, AUC0-24 and AUC0-12 Targets are Met



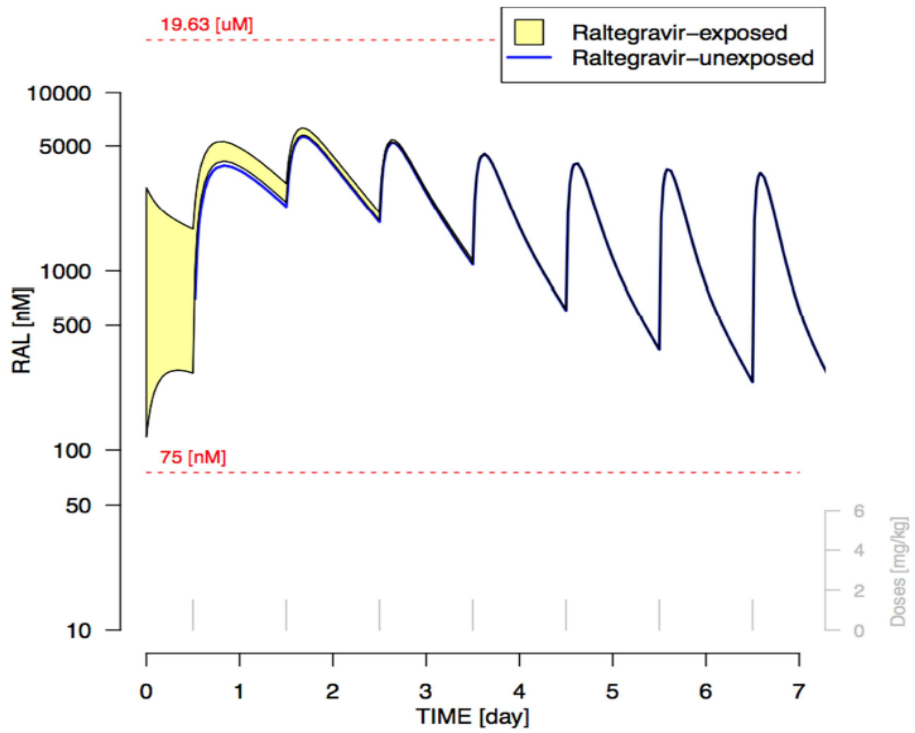
Furthermore, if the first dose in an exposed neonate is administered at 36 h post-partum, the trough concentration should stay above 75 nM and the AUC_{0-24} should stay below 90 µM*hr. If the

first dose in an exposed neonate is given at 12 h post-partum the AUC_{0-24} would likely exceed 90 µM*hr by at most 20% for not more than 2 days.

Figure 10. PK Profiles of Raltegravir-Exposed Neonates After Administration of a First Dose 36 hours post-partum (top) and 12 hours post-partum (bottom)



Birth at TIME=0 (day). First dose administration 36 hours after birth of raltegravir-exposed (yellow area) and 12 hours after birth of 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).

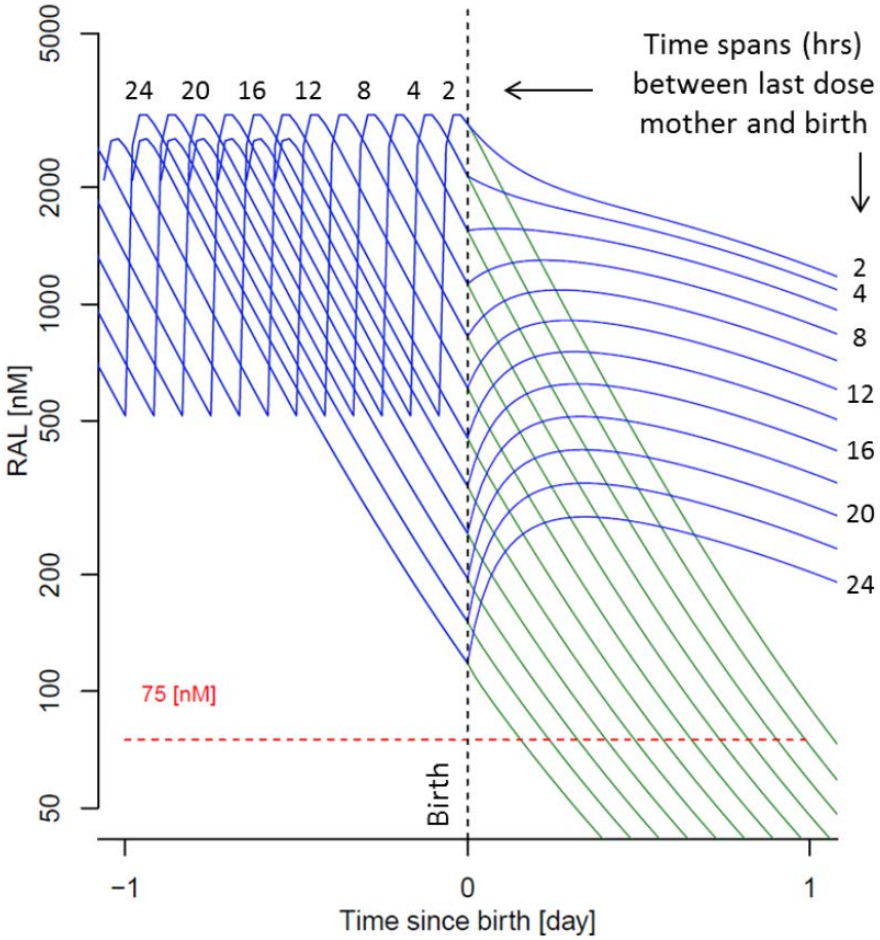


The MAH concluded that the recommended regimen in raltegravir-exposed neonates should be the same as that for unexposed neonates with the modification that if the mother received raltegravir

within 2 to 24 h prior to delivery, the first infant dose should be given between 24 to 48 hours after birth.

The POPPK report provides some relevant simulations. The first figure shows that if the time since last maternal dose was < 6 h the neonatal profile was predicted to decline but if > 6 h had elapsed then there was an initial rise predicted due to back flow from the neonatal peripheral compartment.

Figure 11. Predicted Superimposed Concentration-Time Profiles of Raltegravir (Semilog Scale) in both Mother (green) and Neonate (blue), with Last Dose Administration in time range 2 – 24 hrs before giving birth



The predicted trough and AUC during the first week after birth when applying various assumptions regarding time between last maternal dose and birth (2-24h) are depicted below. The third figure shows the exposures if exposed infants do not receive the first dose until 36 h after birth.

Figure 12. Influence of the Time Span Between the Last Dose Administration to Mother and Birth on Raltegravir Trough Concentrations in the Neonate

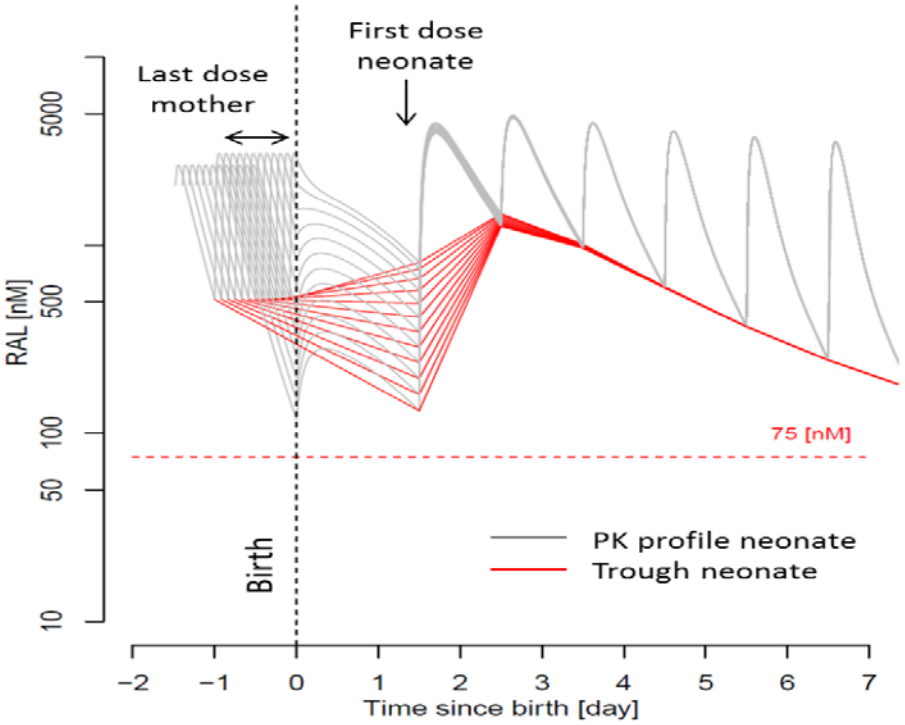
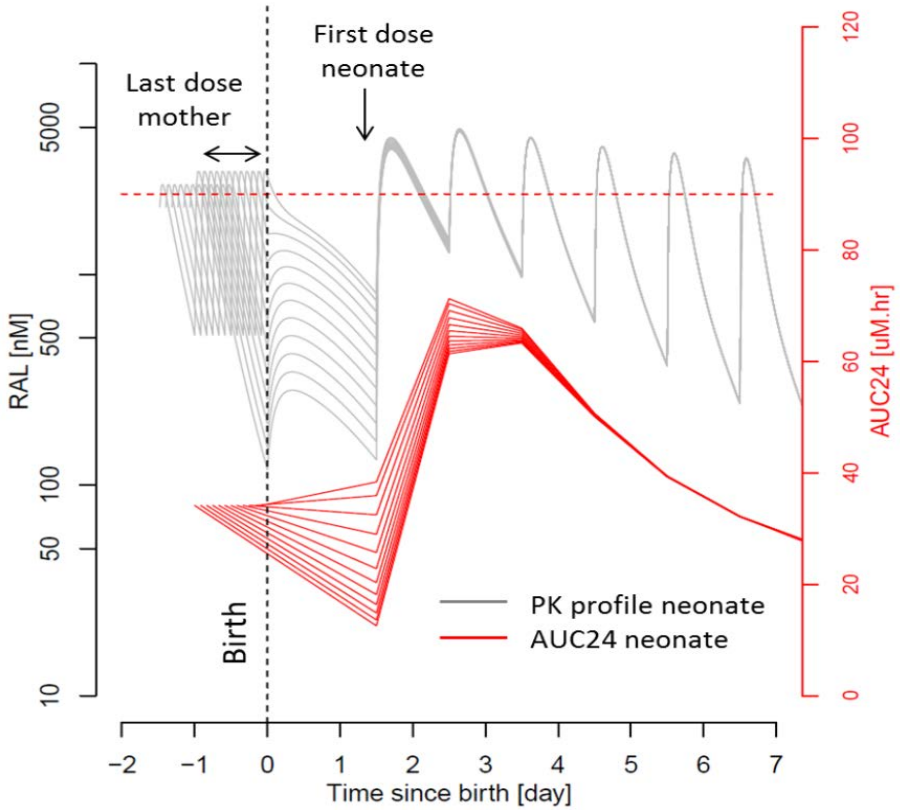
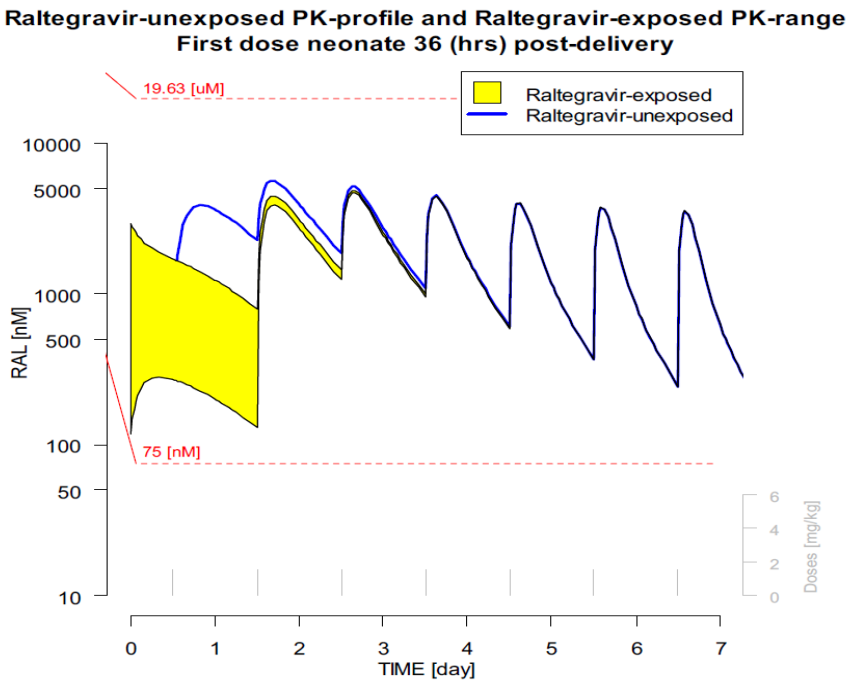


Figure 13. Influence of the Time Span Between the Last Dose Administration to Mother and Birth on Raltegravir AUC0-24 in the Neonate





Dosing tables for neonates

During the conduct of IMPAACT P1110, a letter of amendment was issued to increase the volume for reconstitution of GFS from 5 mL to 10 mL, which gives a concentration of 10 mg/mL. In addition, the GFS dosing tables were simplified to include three weight bands (2 to <3 kg, 3 to <4 kg and 4 to <5 kg). This amendment was implemented at one site and for a single neonate.

Weight band	Week-1 (1.5 mg/kg)	Week 2-4 (3 mg/kg)	Week 5-6 (6 mg/kg)
2 to < 3 kg	4 mg	8 mg	20 mg
3 to < 4 kg	5 mg	10 mg	25 mg
4 to < 5 kg	7 mg	15 mg	30 mg

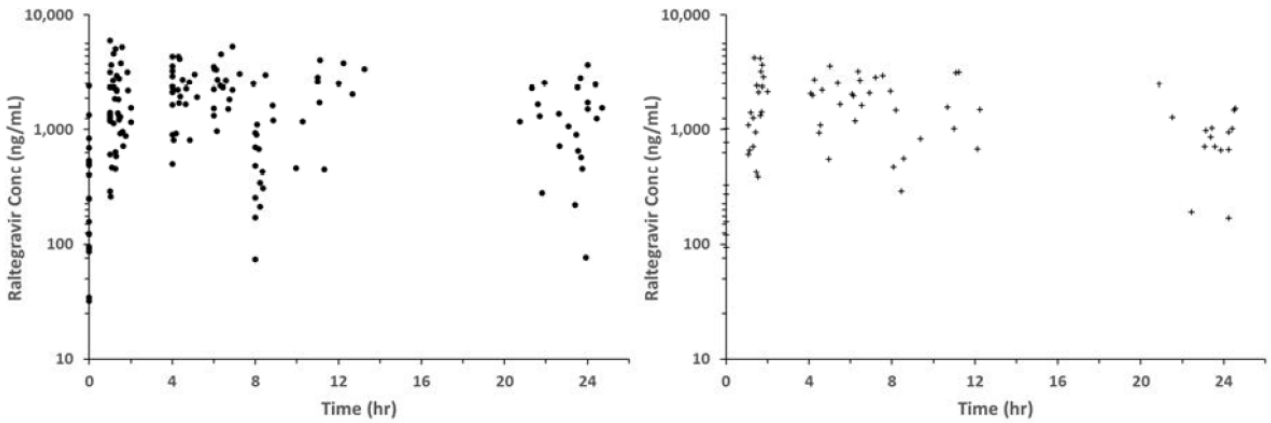
The use of these fixed doses was assessed by simulations of raltegravir-unexposed neonates with body weights corresponding to the lower and upper limits of each weight band using the integrated POPPK model. In all cases the trough concentrations remained above 33 ng/mL (75 nM). Neonates at the lower end of the weight bands were predicted to have raltegravir exposures that exceeded the AUC target after the first dose and at each regimen change to a higher daily dose. The most extreme case was a low weight neonate of predicted to achieve 1.3-fold the AUC_{0-24} criterion for 2 days in Week 1 and 1.2-fold the AUC_{0-12} criterion for 13.5 days.

		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

Food Effect

The CRF recorded if the neonate was fed 1 hour before and/or 1 hour after dosing (classed as dosing under fed conditions in Figure 14). No important effect of food was found.

Figure 14. Individual Raltegravir Concentration-Time Profiles of Raltegravir- Unexposed and Raltegravir-Exposed Neonates Under Fed (Left Panel) or Fasted (Right Panel) Conditions (Cohorts I and II combined)*



Genotyping

The mean oral clearance values (CL/F) observed in Cohort I at PK Visit 1 (raltegravir-unexposed and raltegravir-exposed neonates) and in Cohort II at PK Visits 1 and 4 (all unexposed neonates) in subsets with the mutant ((TA)5/(TA)6, (TA)6/(TA)7 and (TA)7/(TA)7) and wildtype ((TA)6/(TA)6) genotype of UGT1A1 largely overlapped, suggesting that the genotype grouping did not impact on the disposition of raltegravir in neonates.

Figure 15. Summary of Raltegravir CL/F between UGT1A1 Genotype Groups – PK Evaluable Neonates

		Mutant	Wild- Type	Total
First Intensive PK CL/F (L/hr)	n	15	17	32
	mean (std dev)	0.09 (0.06)	0.13 (0.11)	0.11 (0.09)
	min, max	0.02, 0.25	0.01, 0.51	0.01, 0.51
	median	0.08	0.10	0.10
	q1, q3	0.04, 0.12	0.07, 0.13	0.06, 0.13
Second Intensive PK CL/F (L/hr)	n	9	10	19
	mean (std dev)	0.72 (0.40)	0.76 (0.47)	0.74 (0.43)
	min, max	0.42, 1.63	0.30, 1.90	0.30, 1.90
	median	0.56	0.65	0.56
	q1, q3	0.45, 0.76	0.41, 0.98	0.43, 0.98

For UGT1A-1 genotype (presence or absence of *28/*28 genetic variant): Wild-type: 6/6; mutation: any copy that is not 6/6.

Notes: (1) As per the Statistical Analysis Plan, no formal comparisons were done due to small sample size and its limited statistical power.

(2) The second intensive PK CL/F summary includes only Cohort II participants, since only Cohort II had second intensive PK testing.

Abbreviations: CL/F = Apparent clearance following dosing, n = number of neonates contributing both PK and genotype data, PK = pharmacokinetic, q1, q3 = 25th percentile, 75th percentile, std dev = standard deviation

2.4.3. Discussion on clinical pharmacology

General study design and PK targets

To generate safety and PK data to support selection of a dosing schema for neonates (i.e. infants in the first 4 weeks of life) study P080 enrolled neonates at high risk of HIV acquisition via MTCT and they all received raltegravir in addition to standard PMCTC regimens.

In the absence of prior data in neonates and based on what is known about maturation of UGT1A1, Cohort I of the study was given two single doses to generate sufficient PK data to select daily or BID dosing regimens that were to commence within 48 h of birth in Cohort II. Since some mothers had received raltegravir as part of their HIV treatment regimen, the data from neonates in Cohort I who had and had not been exposed to raltegravir *in utero* were analysed separately. All infants in Cohort II had not been exposed to raltegravir *in utero.* Therefore, modelling and simulations were conducted to account for neonatal plasma levels resulting from maternal treatment and determine the most appropriate time after birth to commence daily dosing depending on whether the neonate was exposed *in utero*.

The PK targets set for P080 were based on the targets applied in study P022, in which HIV-1 infected infants and toddlers (4 weeks to <2 years of age) in Cohorts IV and V were dosed using the GFS at 6 mg/kg BID. These targets were previously discussed in detail in the report on X44G. The initial protocol for P022 set a target minimum exposure for each cohort comprising a GM AUC_{0-12} 14-25 µM·hr and concurrent GM C_{12} >33 nM (i.e. the IC_{95}). Additionally, for safety reasons, the maximum AUC_{0-12} was to be <45 µM·hr, which represents half the AUC_{0-24} observed when 1600 mg was administered in Phase I adult studies. Subsequently, the importance of C_{12} for efficacy of raltegravir became clear from study 071, which compared 400 mg BID vs. 800 mg QD in adults and failed to show non-inferiority for QD vs. BID dosing. Therefore, the targets in Cohorts IV and V were modified to GM AUC_{0-12} 14-45 µM·hr and GM C_{12} ≥75 nM.

The actual values achieved in P022 were:

- Cohort IV GM AUC_{0-12} 19.8 uM.hr (34% CV) and GM C_{12} 108.2 nM (52% CV)
- Cohort V GM AUC_{0-12} 22.3 uM.hr (40% CV) and GM C_{12} 116.6 nM (68% CV)

In P080 the PK targets for safety in Cohort I were for individual concentrations to not exceed a Cmax of 8724 ng/mL (19.63 µM; based on the TQT study maximum) and AUC_{12} of 28 hr*mg/L (63.05 µM*hr). In Cohort II, the PK targets were also designed to address efficacy and were aligned with those in P022, i.e.:

- GM AUC_{24} 12 to 40 hr*mg/L (28 to 90 µM*hr) and C_{trough} >33 ng/mL (75 nM) for QD dosing
- GM AUC_{12} 6 to 20 hr*mg/L (14 to 45 µM*hr) and C_{trough} >33 ng/mL (75 nM) for BID dosing

Based on the previous assessment and the safety, efficacy and PK data observed in Cohorts IV and V of P022, the targets used in P080 are appropriate. Since Cohort I infants were receiving a full PMTCT regimen with other agents, and considering what is known about maturation of UGT1a1, it was also appropriate that the initial dose tested was less than that recommended from the age of 4 weeks.

Derivation of the dose regimen for neonates

In Cohort II, the mg/kg doses were derived from simulations using a POPPK model that included data from 6 unexposed infants in Cohort I as well as data from Cohorts IV and V in P022 and infants born to mothers in P1097. Based on observed PK data from 25 unexposed neonates in Cohort II who received 1.5 mg/kg for 7 days (with a first dose within 48 h of birth) the post-first dose GM C_{trough} and AUC_{24} values met the pre-specified targets. The GM C_{trough} greatly exceeded the target (947.9 ng/mL) while the GM AUC_{0-24} (38.20 hr*mg/L) was near to the upper limit. Individual AUC_{0-24} values frequently exceeded 40 hr*mg/L (in 11 individuals; maximum observed was 78 hr*mg/L). In contrast, the POPPK report shows that median C_{trough} decreased >10-fold between day 1 and day 7 of dosing with 1.5 mg/kg QD.

After switching to 3 mg/kg BID the day 15 to 18 GM values were much lower (C_{trough} 557.99 ng/mL and AUC_{0-12} 14.30 hr*mg/L) than observed after the first 1.5 mg/kg dose, indicating the importance of increasing raltegravir clearance in the first 2 weeks of life. After about one week of the 3 mg/kg BID dose at Day 14, 3/9 had AUC_{0-12} above the target (>20 µg.hr/mL) compared to 0% and 9% of Cohorts IV and V in P022. In contrast, up to 27% had trough levels below the target between weeks 2 and 4 while receiving 3 mg/kg BID. Nevertheless, the median Ctrough values at the end of 1.5 mg/kg QD and during 3 mg/kg BID dosing were higher than those documented in Cohorts IV and V of P022.

In infants dosed with 6 mg/kg from 4 weeks of age the C_{trough} in infants in Cohort II of P080 was about twice the values previously observed in Cohorts IV and V of P022. The model-predicted AUC_{0-12} values indicated that 41% in P080 would exceed the AUC_{0-12} criterion in weeks 5-6 compared to none in Cohorts IV and V of P022.

The dose regimen used in Cohort II of P080 potentially over-exposes neonates during initial dosing with 1.5 mg/kg QD and again during dosing with 3 mg/kg BID and 6 mg/kg BID. There is a dramatic drop in C_{trough} in the first week of life, supporting a change in regimen at least by day 7 of life. The 3 mg/kg BID dose from weeks 1 to 4 of life results in a predicted 41% over-exposed based on AUC_{0-12} but at the same time up to 27% are under-exposed based on C_{trough}. It seems there is very considerable inter-individual variation and it may not be possible to overcome the impact of variable and rapidly changing raltegravir clearance in the first month of life. The CHMP accepted that the overall proposed regimen is likely to be the best that can be achieved whilst still being practical.

Time of the first dose in raltegravir-exposed neonates

Raltegravir is indicated only for treatment of HIV-1. It is not indicated for use in PMTCT regimens. Very few neonates are likely to be confirmed to have acquired HIV and be started on treatment within 1-2 days of birth. Nevertheless, it is acceptable that recommendations are provided in case raltegravir is considered for inclusion in the neonatal primary treatment regimen.

The SmPC additions in section 4.2 for dosing neonates do not make any statement about the minimum time from birth that treatment could start except in case of neonates exposed to raltegravir *in utero*, in which case the first dose is to be given between 24 and 48 h after birth if the mother took raltegravir 2 to 24 hours before delivery. This minimum 24 h limit post-birth for starting raltegravir in exposed neonates was not imposed in P080 but has been derived from modelling.

The actual data from Cohort I neonates who had been exposed to raltegravir *in utero* and received a single dose of 1.5 mg/kg within 22-45 h of birth showed that 4/6 exceeded the AUC_{0-12} <28 hr*mg/L target, although not by much (maximum value was 34.66 hr*mg/L) while C_{trough} varied hugely from 12-1324 ng/mL. The final recommendation to give the first dose of 1.5 mg/kg between 24 and 48 hours postpartum is based on predicted C_{trough} > 33 ng/mL and AUC_{0-24} < 40 mg*hr/mL. The simulations generally support this advice and suggest that there is sufficient forgiveness in the modelling that it is not necessary to impose a specific 36-h minimum time limit.

Simplified dosing table in 4.2

The MAH's proposals for the SmPC for neonates are:

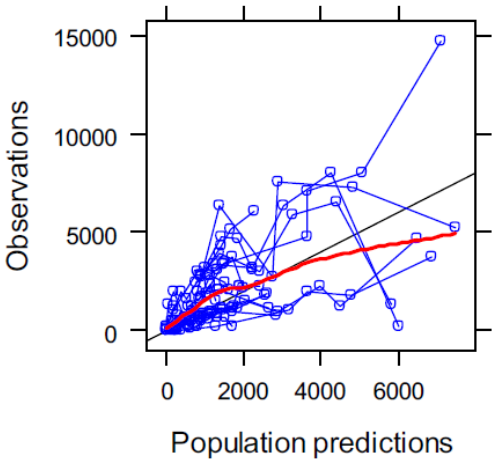
- Based on weight bands and not on mg/kg dosing as used in Cohort II of P080
- Separated depending on weight band dosing from birth to week 1 or from 1-4 weeks

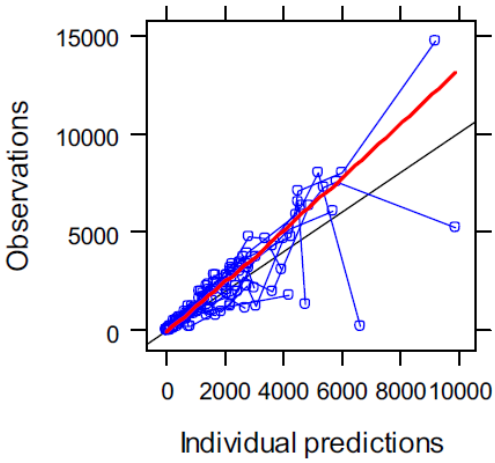
At the time of approval of the GFS for use from 4 weeks of age the EU SmPC was aligned with that of the US FDA in using a simplified dosing table by weight band that closely approximated to 6 mg/kg but avoided the need to calculate the dose once the infant weight was known. The MAH is proposing a similar weight banding approach for neonates based on simulations. It appears that the simulations predict 100% of values exceeding the required trough value and only modest increases over the AUC criteria.

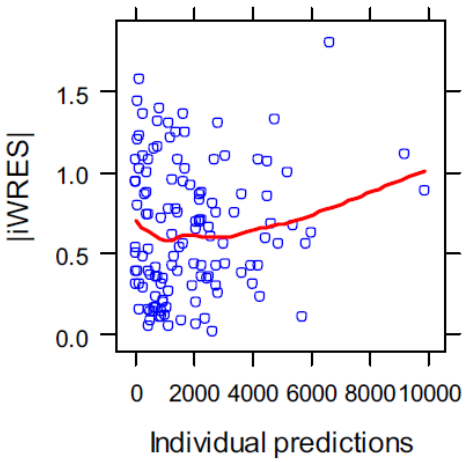
POPPK models

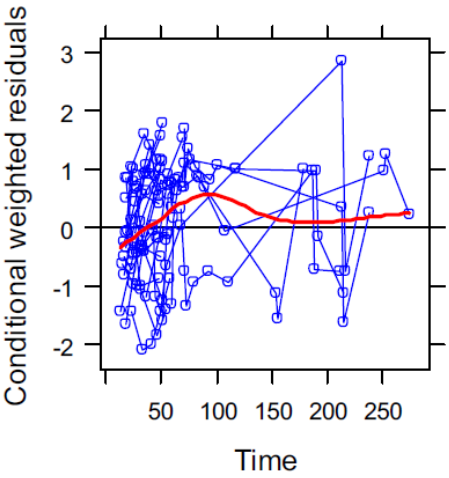
The interim model is complex and is considered useful to support the proposed posology. The overall fit to the model is reasonable for the infants unexposed *in utero.* The diagnostic plots for the integrated model in infants exposed to raltegravir *in utero* show (see run205) evidence of model misspecification and residuals do not appear to be distributed around zero. This initially raised doubt on the reliability of the model to support dosing in exposed individuals; however it should be noted that the deviations are at extreme values and are suggested to be due to the limitations of the sparse data available. Other plots suggest that the model is robust.

Raltegravir-Exposed, run205

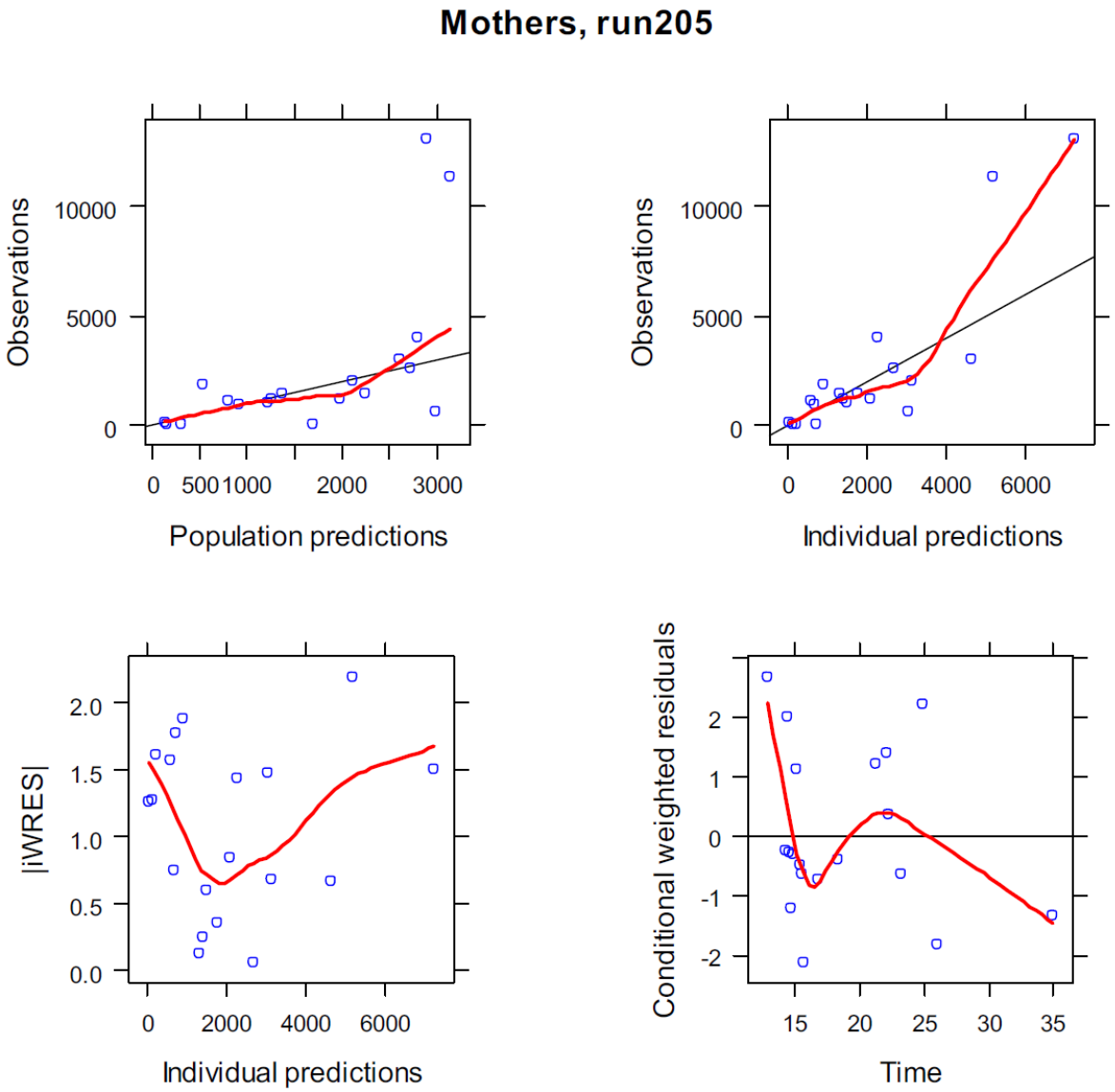




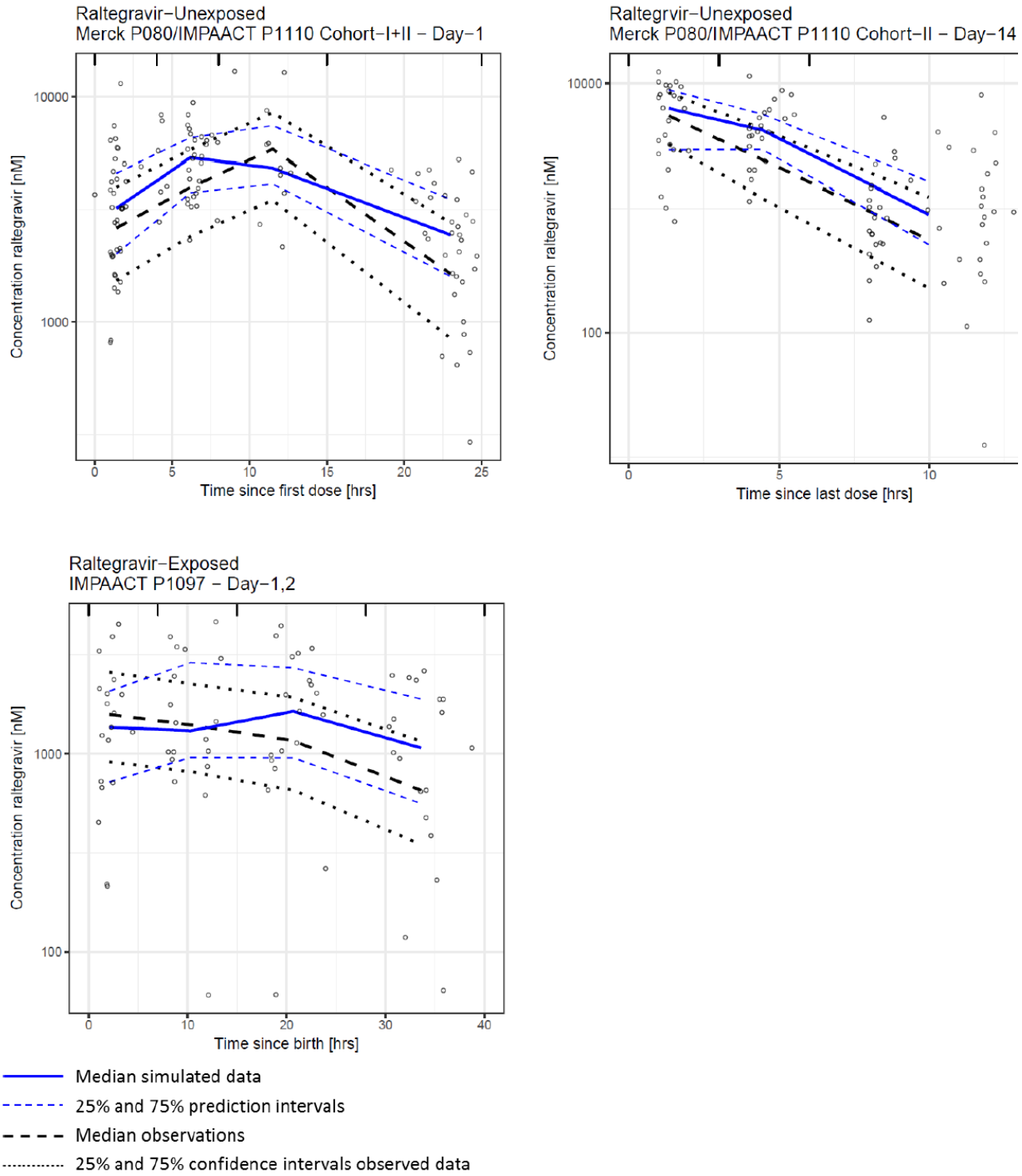




Goodness-of-fit Plots on the Integrated Mother-Neonate Population PK Model in Linear Scale



Visual Predictive Checks Plots on the Integrated Mother-Neonate Population PK Model by Cohort in Semilog Scale



Doubling the administration volume

At the same time as introducing posology for neonates, the MAH is amending the existing table for dosing of infants from 4 weeks of age to double the volumes to be administered, reflecting a change in the volume into which the GFS are suspended. The idea is to make it easier to measure out the required dose and to use the same dilution instructions for dosing infants < and > 4 weeks.

In support of the use in neonates the MAH proposed an update to the packaging and kit components (including the suspension volume) to facilitate accurate measurement of the smaller doses required for neonates, the proposed kit is based upon the existing configuration, for which there have been no adverse event reports related to its use. Usability studies were carried out.

Initially, the CHMP raised the issue about transition to the new kit, as there is the concern that (i) treatment centres that already use the GFS in infants from 4 weeks of age could fail to appreciate that the new (replacement) dosing table for this age group reflects new dilution instructions, which could inadvertently lead to administering twice the recommended dose, (ii) Treatment centres that start to treat neonates could fail to appreciate the new dilution instructions so that neonates could be inadvertently overdosed due to administration of the recommended volumes but using the current dilution strategy. Both errors could result in administration of twice the recommended dose. For that reason, a booklet, containing step-by-step instructions for use, colored pictograms and understandable text is included along with the package leaflet within the product packaging of the granules for oral suspension. Furthermore, the inclusion of 3 different syringes of different colours in the pack (10ml is blue, 3ml is green and 1ml is white) will allow correct measurement of the dose.

2.4.4. Conclusions on clinical pharmacology

The dosing regimens in neonates are based on weight band dosing from birth to week 1 or from 1-4 weeks. The proposed dose regimens used in Cohort II of P080 might be the best that can be achieved whilst still being practical.

2.5. Clinical efficacy

The study was not designed to evaluate the efficacy of raltegravir as a component of prophylaxis or treatment in HIV-1 exposed neonates at high risk of acquiring HIV-1 infection. Neonates and infants in this study were tested for evidence of HIV-1 infection, as part of standard clinical monitoring of HIV-1 exposed neonates. None had a positive HIV-1 test when assessed at birth, 6 or 24 weeks of age.

2.6. Clinical safety

Patient exposure

Overall, 42 neonates received at least 1 dose of raltegravir (16 in Cohort I and 26 in Cohort II). In Cohort II neonates received 1.5 mg/kg once daily for a mean of 6 days, 3 mg/kg twice daily for mean of 22 days and 6 mg/kg twice daily for a mean of 13.13 days. The maximum duration did not exceed 43 days.

In Cohort I, the most frequently reported (≥10%) clinical AEs through 6 weeks were vomiting (3), nasal congestion (2) and pallor (2). In Cohort II, the most frequently reported (≥10%) AEs through 6 weeks were oral candidiasis (6), jaundice neonatal (4), congenital umbilical hernia (3), cough (3) and nasal congestion (3).

Most clinical AEs were of Grade 1 or Grade 2. In Cohort I, Grade 3 or greater clinical AEs were reported in 2 neonates but both occurred after completion of dosing. One had Grade 4 neonatal anaemia (SAE). In Cohort II, Grade 3 or greater clinical AEs were reported in 2 infants. One had Grade 3 and one had Grade 3 weight decreased, which were SAEs.

Table 12. Extent of exposure of cohort II neonates to raltegravir by dose

RAL	≤1 Week	>1 Week to ≤2Weeks	>2 Weeks to ≤3 Weeks	>3 Weeks to ≤4 Weeks	>4 Weeks to ≤5 Weeks	>5 Weeks to ≤6 Weeks	>6 Weeks	Total subjects	Duration Range	Mean Duration
Any dose	1	1	0	0	1	21	2	26	1 to 43 days	37.69 days
1.5 mg/kg QD	24	1	0	0	0	0	0	25	1 to 8 days	6 days
3 mg/kg BID	1	0	1	22	0	0	0	24	7 to 28 days	22 days
6 mg/kg BID	1	18	5	0	0	0	0	24	3 to 17 days	13.13 days

Although neonates received different raltegravir dosages, they have been counted only one time each, on the 'ANY DOSE' row.
Abbreviations: BID = twice daily, QD = once daily, RAL = raltegravir

Adverse events

Through 6 Weeks

The table summarises the safety profile observed. There were no drug-related clinical AEs reported through 6 weeks of age in Cohorts I or II, but there were drug-related laboratory AEs.

Table 13. Summary of Clinical Adverse Events through 6 Weeks of Life - All Treated Neonates

	Cohort I				Cohort II	
	RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)		RAL unexposed (N=26)	
	n (%)	n (%)	n (%)	90% C.I.	n (%)	90% C.I.
With one or more clinical adverse events	7 (70)	4 (66.7)	11 (68.8)	(45.2, 86.8)	19 (73.1)	(55.3, 86.6)
With no clinical adverse event	3 (30)	2 (33.3)	5 (31.3)	(13.2, 54.8)	7 (26.9)	(13.4, 44.7)
With one or more serious clinical adverse events	1 (10)	1 (16.7)	2 (12.5)	(2.3, 34.4)	2 (7.7)	(1.4, 22.3)
With one or more serious drug related* clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	(0, 17.1)	1 (3.8)	(0.2, 17)
With one or more Grade 3 or greater clinical adverse events	1 (10)	1 (16.7)	2 (12.5)	(2.3, 34.4)	2 (7.7)	(1.4, 22.3)
With one or more Grade 3 or greater drug related* clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)

Serious adverse events included ICH defined serious adverse events and malignancies.
*Drug related adverse events were determined by the protocol team to be possibly, probably or definitely related to RAL.
Abbreviations: CI = confidence interval, ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, N = number of neonates in each cohort, n (%) = number (percent) of neonates in each subcategory, RAL = raltegravir

Table 14. All Clinical Adverse Events through 6 Weeks of Life by System Organ Class - All Treated Neonates

	Cohort I			Cohort II
System Organ Class Preferred Term	RAL unexposed (N=10) n (%)	RAL exposed (N=6) n (%)	Total (N=16) n (%)	RAL unexposed (N=26) n (%)
Number of neonates with one or more adverse events	7 (70)	4 (66.7)	11 (68.8)	19 (73.1)
Blood and lymphatic system disorders	0 (0)	1 (16.7)	1 (6.3)	1 (3.8)
Anaemia neonatal	0 (0)	1 (16.7)	1 (6.3)	1 (3.8)
Cardiac disorders	0 (0)	0 (0)	0 (0)	1 (3.8)
Cyanosis	0 (0)	0 (0)	0 (0)	1 (3.8)
Congenital, familial and genetic disorders	1 (10)	0 (0)	1 (6.3)	6 (23.1)
PPD	1 (10)	0 (0)	1 (6.3)	0 (0)
Congenital megaureter	0 (0)	0 (0)	0 (0)	1 (3.8)
Congenital renal cyst	0 (0)	0 (0)	0 (0)	1 (3.8)
PPD	0 (0)	0 (0)	0 (0)	1 (3.8)
Congenital umbilical hernia	0 (0)	0 (0)	0 (0)	3 (11.5)
Pulmonary artery stenosis congenital	1 (10)	0 (0)	1 (6.3)	0 (0)
Eye disorders	0 (0)	0 (0)	0 (0)	1 (3.8)
Conjunctival hyperaemia	0 (0)	0 (0)	0 (0)	1 (3.8)
Eye discharge	0 (0)	0 (0)	0 (0)	1 (3.8)
Gastrointestinal disorders	3 (30)	2 (33.3)	5 (31.3)	6 (23.1)
Constipation	0 (0)	0 (0)	0 (0)	1 (3.8)
Flatulence	0 (0)	0 (0)	0 (0)	1 (3.8)
Infantile colic	0 (0)	0 (0)	0 (0)	1 (3.8)
Infantile vomiting	0 (0)	0 (0)	0 (0)	2 (7.7)
Oral mucosal discolouration	0 (0)	1 (16.7)	1 (6.3)	0 (0)
Umbilical hernia	1 (10)	0 (0)	1 (6.3)	0 (0)
Vomiting	2 (20)	1 (16.7)	3 (18.8)	2 (7.7)
General disorders and administration site conditions	1 (10)	1 (16.7)	2 (12.5)	2 (7.7)
Inflammation	0 (0)	0 (0)	0 (0)	1 (3.8)
Pyrexia	1 (10)	0 (0)	1 (6.3)	2 (7.7)
Vessel puncture site bruise	0 (0)	1 (16.7)	1 (6.3)	0 (0)
Hepatobiliary disorders	2 (20)	0 (0)	2 (12.5)	1 (3.8)
Hyperbilirubinaemia neonatal	1 (10)	0 (0)	1 (6.3)	0 (0)

Jaundice	1 (10)	0 (0)	1 (6.3)	1 (3.8)
Infections and infestations	1 (10)	1 (16.7)	2 (12.5)	10 (38.5)
Body tinea	0 (0)	0 (0)	0 (0)	1 (3.8)
Folliculitis	1 (10)	0 (0)	1 (6.3)	0 (0)
Genital candidiasis	0 (0)	0 (0)	0 (0)	2 (7.7)
Oral candidiasis	0 (0)	1 (16.7)	1 (6.3)	6 (23.1)
Skin candida	0 (0)	0 (0)	0 (0)	1 (3.8)
Upper respiratory tract infection	0 (0)	0 (0)	0 (0)	2 (7.7)
Investigations	1 (10)	0 (0)	1 (6.3)	3 (11.5)
Blood pressure increased	1 (10)	0 (0)	1 (6.3)	1 (3.8)
Cardiac murmur	0 (0)	0 (0)	0 (0)	1 (3.8)
Weight decreased	0 (0)	0 (0)	0 (0)	1 (3.8)
Pregnancy, puerperium and perinatal conditions	0 (0)	0 (0)	0 (0)	4 (15.4)
Jaundice neonatal	0 (0)	0 (0)	0 (0)	4 (15.4)
Reproductive system and breast disorders	1 (10)	0 (0)	1 (6.3)	0 (0)
Penile erythema	1 (10)	0 (0)	1 (6.3)	0 (0)
Respiratory, thoracic and mediastinal disorders	3 (30)	0 (0)	3 (18.8)	5 (19.2)
Cough	0 (0)	0 (0)	0 (0)	3 (11.5)
Nasal congestion	2 (20)	0 (0)	2 (12.5)	3 (11.5)
Rhinorrhoea	1 (10)	0 (0)	1 (6.3)	0 (0)
Sneezing	0 (0)	0 (0)	0 (0)	1 (3.8)
Skin and subcutaneous tissue disorders	1 (10)	1 (16.7)	2 (12.5)	6 (23.1)
Dermatitis allergic	0 (0)	0 (0)	0 (0)	1 (3.8)
Dermatitis atopic	0 (0)	0 (0)	0 (0)	1 (3.8)
Dermatitis diaper	0 (0)	1 (16.7)	1 (6.3)	0 (0)
Erythema	0 (0)	0 (0)	0 (0)	1 (3.8)
Milia	0 (0)	0 (0)	0 (0)	1 (3.8)
Papule	1 (10)	0 (0)	1 (6.3)	0 (0)
Rash	0 (0)	0 (0)	0 (0)	2 (7.7)
Seborrhoeic dermatitis	0 (0)	0 (0)	0 (0)	2 (7.7)
Vascular disorders	1 (10)	2 (33.3)	3 (18.8)	2 (7.7)
Hypertension neonatal	1 (10)	0 (0)	1 (6.3)	0 (0)
Pallor	0 (0)	2 (33.3)	2 (12.5)	2 (7.7)

Adverse event terms are from MedDRA Version 19.1.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of neonates in each cohort, n (%) = number (percent) of neonates in each subcategory, RAL = raltegravir

Table 15. Summary of Laboratory Adverse Events through 6 Weeks of Life - All Treated Neonates

	Cohort I				Cohort II	
	RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)		RAL unexposed (N=26)	
	n (%)	n (%)	n (%)	90% C.I.	n (%)	90% C.I.
With one or more laboratory adverse events	9 (90)	6 (100)	15 (93.8)	(73.6, 99.7)	21 (80.8)	(63.7, 92.1)
With no laboratory adverse event	1 (10)	0 (0)	1 (6.3)	(0.3, 26.4)	5 (19.2)	(7.9, 36.3)
With one or more serious laboratory adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	1 (3.8)	(0.2, 17)
With one or more serious drug related* laboratory adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Who died due to laboratory adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	(0, 17.1)	1 (3.8)	(0.2, 17)
With one or more Grade 3 or greater laboratory adverse events	1 (10)	2 (33.3)	3 (18.8)	(5.3, 41.7)	5 (19.2)	(7.9, 36.3)
With one or more Grade 3 or greater drug related* laboratory adverse events	1 (10)	0 (0)	1 (6.3)	(0.3, 26.4)	0 (0)	(0, 10.9)

Serious adverse events included ICH defined serious adverse events and malignancies.
*Drug related adverse events were determined by the protocol team to be possibly, probably or definitely related to RAL.
Abbreviations: CI = confidence interval, ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, N = number of neonates in each cohort, n (%) = number (percent) of neonates in each subcategory, RAL = raltegravir

Table 16. All Laboratory Adverse Events through 6 Weeks of Life - All Treated Neonates

	Cohort I			Cohort II
	RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)	RAL unexposed (N=26)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Number of neonates with one or more adverse events	9 (90)	6 (100)	15 (93.8)	21 (80.8)
Investigations	9 (90)	6 (100)	15 (93.8)	21 (80.8)
Blood alkaline phosphatase increased	0 (0)	1 (16.7)	1 (6.3)	1 (3.8)
Blood bilirubin increased	1 (10)	1 (16.7)	2 (12.5)	5 (19.2)
Blood calcium increased	0 (0)	0 (0)	0 (0)	1 (3.8)
Blood creatinine increased	1 (10)	0 (0)	1 (6.3)	4 (15.4)
Blood glucose decreased	0 (0)	1 (16.7)	1 (6.3)	1 (3.8)
Blood potassium increased	0 (0)	0 (0)	0 (0)	1 (3.8)
Blood sodium decreased	1 (10)	0 (0)	1 (6.3)	0 (0)
Haemoglobin decreased	4 (40)	4 (66.7)	8 (50)	17 (65.4)
Neutrophil count decreased	6 (60)	2 (33.3)	8 (50)	3 (11.5)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of neonates in each cohort, n (%) = number (percent) of neonates in each subcategory, RAL = raltegravir

In Cohort I, one neonate had a drug-related laboratory AE of neutrophil count decreased. The investigator considered this non-serious AE as possibly related to all antiretroviral agents in the regimen (raltegravir, 3TC, NVP and ZDV). The neutrophil count decreased was Grade 3 on day 8 (day of the second dose), increased to Grade 4 on day 13 and decreased to Grade 1 at day 20. In Cohort II, 2 infants had drug-related non-serious laboratory AEs of blood bilirubin increased, which were < Grade 3.

Through 24 Weeks

The table summarises the safety profile observed. There were no drug-related clinical AEs reported through 24 weeks of age in Cohort I or Cohort II.

Table 17. Summary of Clinical Adverse Events through 24 Weeks of Life - All Treated Neonates

	Cohort I				Cohort II	
	RAL unexposed (N=10)	RAL exposed (N=6)	Total (N=16)		RAL unexposed (N=26)	
	n (%)	n (%)	n (%)	90% C.I.	n (%)	90% C.I.
With one or more clinical adverse events	8 (80)	4 (66.7)	12 (75)	(51.6, 91)	23 (88.5)	(72.8, 96.8)
With no clinical adverse event	2 (20)	2 (33.3)	4 (25)	(9, 48.4)	3 (11.5)	(3.2, 27.2)
With one or more serious clinical adverse events	1 (10)	1 (16.7)	2 (12.5)	(2.3, 34.4)	6 (23.1)	(10.6, 40.5)
With one or more serious drug related* clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	(0, 17.1)	1 (3.8)	(0.2, 17)
With one or more Grade 3 or greater clinical adverse events	1 (10)	1 (16.7)	2 (12.5)	(2.3, 34.4)	6 (23.1)	(10.6, 40.5)
With one or more Grade 3 or greater drug related* clinical adverse events	0 (0)	0 (0)	0 (0)	(0, 17.1)	0 (0)	(0, 10.9)

N = Number of neonates in each cohort.
n (%) = Number (percent) of neonates in each subcategory.
90% C.I. = 90% Confidence Interval.
Serious adverse events included ICH defined serious adverse events and malignancies.
*Drug related adverse events were determined by the protocol team to be possibly, probably or definitely related to RAL.

In Cohorts I and II, the reported clinical AEs were generally similar to those seen through 6 weeks. In Cohort II, the most frequently reported AEs through 24 weeks were oral candidiasis (8), cough (8), pyrexia (7), URTI (5), nasal congestion (5), jaundice neonatal (4), seborrheic dermatitis (4), congenital umbilical hernia (3), vomiting (3) and rash (3).

Most clinical AEs were either Grade 1 or Grade 2. In Cohort I, there were no additional subjects with a Grade 3 or greater clinical AE reported. In Cohort II, Grade 3 or greater clinical AEs were reported in 6 infants by 24 weeks. Of the additional AEs reported between weeks 6 and 24, bacterial pneumonia, bronchiolitis, cellulitis and craniocerebral injury were also reported as SAEs.

There were no additional drug-related laboratory AEs reported between 6 weeks and 24 weeks in either Cohort.

Adverse Events of Special Interest (AESIs)

Hyperbilirubinemia
In Cohort I, bilirubin elevations included 1 Grade 1 and 1 Grade 2. The Grade 1 bilirubin elevation occurred on day 39 and the Grade 2 bilirubin elevation occurred on day 35. Both had onset after last dose of raltegravir and resolved. The infant with Grade 2 bilirubin elevation also had bilirubin values ≥10 and <16 mg/dL on days 3, 5, 7 and 9. Both had normal bilirubin values at 24 weeks of age.

In Cohort II, bilirubin elevations included 4 Grade 1, 1 Grade 2 and 1 Grade 4, all of which resolved. The onset of graded bilirubin elevations was prior to or at 14 days of age in 3/6 cases. The Grade 4 bilirubin elevation occurred on day 16 in a neonate who discontinued study therapy due to a clinical AE. Neither phototherapy nor exchange transfusion was used in any cases and there was no association with Grade 3 or 4 elevations in ALT or AST because there were no such events reported.

In evaluating the potential association between neonatal hyperbilirubinemia and genotype, the assessment from birth through 14 days was considered the most clinically relevant. Despite a reasonable distribution of non-wild type genotypes, the low incidence of hyperbilirubinaemia meant that the data could not support an assessment of any association between hyperbilirubinemia and UGT1A1 or *SLCO1B3* genotype.

Metabolic Disorders
There were no AEs in the system organ class of metabolism and nutrition disorders reported through 6 weeks of age but by 24 weeks there were AEs of dehydration (Grade 2), failure to thrive (Grade 3) and malnutrition (Grade 4) reported for an infant in Cohort II who had previously discontinued study therapy and was noted to have weight loss, early vomiting and gastroesophageal reflux.

Gastrointestinal Disorders
AEs in the SOC gastrointestinal disorders in the first 6weeks were primarily vomiting in Cohort I (3) and Cohort II (2), which were Grade 1 or 2 and were not treatment-limiting. No AEs of gastritis were reported. AEs in this SOC by 24 weeks of age were generally similar to those reported by 6 weeks.

Rash
AEs of rash were reported in 2 infants in Cohort II through 6 weeks of age. Both were Grade 1. There were also single reports of dermatitis allergic (Grade 2) and dermatitis atopic (Grade 1) in Cohort II. None was serious, drug-related or resulted in discontinuation of study therapy. There were 2 additional cases of rash reported by 24 weeks and an additional case of dermatitis allergic. These were Grade 1 or 2, non-serious and not drug-related.

Congenital anomalies
There were no congenital anomalies reported for the 6 Cohort I neonates who were exposed to raltegravir *in utero*.

Serious adverse event/deaths/other significant events

There were no deaths in the study. SAEs were based on data entered by the site/investigator onto a DAIDS Expedited Adverse Event (EAE) form, which was submitted to the DAIDS Regulatory Compliance Center (RCC), and subsequently provided to the IMPAACT Statistical Data Analysis Center for reporting purposes. The tables only include SAEs that met the criteria in the DAIDS EAE reporting manual.

Through 6 Weeks

In Cohort I, 2 neonates had SAEs of Grade 4 neonatal anaemia on day 22, which decreased in severity and ended on day 170, and Grade 1 vomiting on days 2 through 3 of age.

In Cohort II, 2 infants had serious clinical AEs reported through 6 weeks. None was drug-related. Grade 3 weight decreased was reported from day 29 through day 86 and led to discontinuation of study therapy. One had a SAE of blood glucose decreased, which was Grade 3 AE was not drug-related.

Through 24 Weeks

In Cohort I, there were no additional serious clinical AEs reported through 24 weeks of age. In Cohort II, 4 infants had SAEs with onset between 6 and 24 weeks, including bronchiolitis (2), cellulitis (1; also had bronchiolitis), pneumonia (1) and craniocerebral injury (1). All SAEs were Grade 3 in severity and none was drug-related. The cellulitis was ongoing at the final study visit but the others had resolved. There were no additional serious laboratory AEs reported.

Laboratory findings

The review of all laboratory values out of normal limits and changes from baseline did not add to the information provided above on laboratory abnormalities that were reported as AEs.

Discontinuation due to adverse events

In Cohort I, there were no clinical AEs that led to discontinuation of study therapy. In Cohort II, one infant had a clinical SAE of Grade 3 weight decreased (see above) that led to discontinuation of study therapy on day 31. This infant had vomiting reported on day 7. Grade 1 jaundice was reported on days 8 through 29 with the laboratory AE of Grade 4 blood bilirubin increased reported on day 16. Grade 2 weight decreased was reported on days 16 through 29 and Grade 3 weight decreased was reported on days 29 through 86. After discontinuing study therapy, the infant was diagnosed with malnutrition (Grade 4) and failure to thrive (Grade 3) on day 53 and with GERD on day 80. These AEs resolved and none was drug-related.

2.6.1. Discussion on clinical safety

The safety data to support neonatal use are limited to 26 neonates/infants who received 1-43 (mean 38 days) raltegravir in Cohort II plus 16 neonates who received 2 separated single doses in Cohort I. The safety data should also be viewed against the background variable PMTCT regimens and the lack of a placebo control group. There were no drug-related clinical AEs and few drug-related laboratory AEs. There is a theoretical risk that raltegravir could exacerbate neonatal hyperbilirubinaemia and appropriate wording is included in section 4.8 of the SmPC.

2.6.2. Conclusions on clinical safety

There are no new major concerns arising from the safety data reported from study P080. All adverse drug reactions are included in section 4.8.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version V14 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version V14 with the following content:

Safety concerns

Important Identified Risks	Immune reconstitution inflammatory syndrome Drug resistance Drug interaction with rifampin and other strong UGT1A1 inducers Extent of pharmacokinetic (PK) variability and impact, if any, on pharmacodynamics (PD) Serious Rash Drug interaction with metal cation containing antacids Increase in CPK with clinical manifestations; myopathy, rhabdomyolysis
Important Potential Risks	Malignancies Increase in liver enzymes Depression, suicidal ideation, suicidal behaviors **Medication error related to 1) potential substitution of the**

	pediatric formulations for the 400mg film-coated tablet (pediatric formulations and the 400mg film-coated tablet are not bioequivalent) 2) potential substitution of one film-coated tablet for the other, 3) potential for dosing errors in neonates
Important Missing Information	Safety of 1200 mg QD (2x600mg tablets) dosing in pregnant women Safety in lactating women Safety in preterm (<37 weeks gestation) or low birth weight (<2000 grams) neonates Safety in elderly patients Safety in patients with severe hepatic impairment

Pharmacovigilance plan

The Pharmacovigilance plan was not changed within this extension of indication.

Risk minimisation measures

The Risk minimisation measures related to medication error were updated as follows:

Safety Concern	**Routine Risk Minimization Measures**	**Additional Risk Minimization Measures**
Medication Error related to 1) potential substitution of the pediatric formulations for the 400 mg film-coated tablet (given pediatric formulations and the 400mg film-coated tablet are not bioequivalent) 2) potential substitution of one film-coated tablet for the other, 3) Potential for dosing errors in neonates	Listed in SmPC Section 4.2, Posology and method of administration, of the SPC. Package leaflet—Section 3, How to take Isentress. A booklet, containing step-by-step instructions for use, colored pictograms and understandable text is included along with the package leaflet as separate packaging components within the product packaging of the granules for oral suspension.	None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Further, the MAH proposed to update the suspension volume from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurement of the smaller doses required for neonates. As a consequence, sections 6.5 and 6.6 of the SmPC have been updated and the labelling and

instructions for use in the Package Leaflet have been updated accordingly.

2.8.1. User consultation

A statement on the user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Favourable effects

Raltegravir was shown to be effective for the treatment of HIV-1 in adults. Subject to identification of suitable dose regimens for children it could be expected that raltegravir would contribute to the overall efficacy of a regimen to the same extent as observed in adults. In this regard, it is relevant to note that the virological responses observed in study 022, including the two youngest age groups (Cohorts IV and V), were in line with data obtained in treatment-experienced adults.

3.2. Uncertainties and limitations about favourable effects

Study 080 did not enrol HIV-1-infected neonates and P022 was not designed to provide definitive efficacy data. The expectation of efficacy is based on pharmacokinetic data demonstrating that age and weight-specific dose regimens maintain plasma levels above the target C_{trough} derived from study 071 in adults. The actual data and the predicted values in P080 indicate that most neonates should achieve and maintain values above the target C_{trough} criterion subject to adequate adherence.

It seems there is very considerable inter-individual variation and it may not be possible to overcome the impact of variable and rapidly changing raltegravir clearance in the first month of life. The CHMP accepted that the overall proposed regimen is likely to be the best that may be achieved whilst still being practical.

3.3. Unfavourable effects

At present the data suggest a comparable safety profile in children aged < 2 years as has been observed in older children, adolescents and adults. There are no new concerns raised.

3.4. Uncertainties and limitations about unfavourable effects

The numbers of subjects aged < 18 years exposed to raltegravir are very limited and the duration of reporting is relatively short for the subjects aged < 2 years. There were only 26 neonates exposed to multiple dosing in P080 and there is no control group that received PMTCT alone. The longer-term data from the older children in P022 do not currently suggest the onset of new AEs emerging with time but the maximum duration of dosing in P080 was 6 weeks because none of the neonates enrolled was found to have acquired HIV.

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

The favourable effects for raltegravir use in infants have not been directly studied but the PK data suggest that adequate trough concentrations are likely to be reached in the majority to infer that raltegravir will contribute when used as part of an appropriate treatment regimen in this age group.

There is no indication of any new or special concerns pertinent to use of raltegravir in neonates but the data are very limited and a possible increase in hyperbilirubinaemia cannot be dismissed.

3.5.2. Balance of benefits and risks

The benefit-risk balance for use of raltegravir in neonates is favourable and the proposed dose regimens are considered adequate for the small population that could benefit in the EU.

3.6. Conclusions

The overall B/R of Isentress is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA, IIIB and Annex A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of HIV-1 exposed neonates (under the age of 4 weeks) based on safety and PK data from one pivotal Phase 1 study, IMPAACT P1110 (Protocol 080), in a total of 42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and ≥2000 g), who received either 2 single doses of oral suspension, within 48 hours of birth and Day 7-10 of age (Cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (Cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, the suspension volume has been updated from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurement of the smaller doses required for neonates. As a consequence, the 5 mL syringe previously supplied in the presentation for granules for oral suspension is replaced with 3 new oral dosing syringes of various sizes (1 mL, 3 mL, and 10 mL), from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC have been updated and the labelling and instructions for use in the Package Leaflet and the Annex A have been updated accordingly. An updated RMP version 14.0 was agreed during the procedure.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0155/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.