CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205786Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY SECONDARY REVIEW

NDA#	205786, 203045 S-009, 22145 S-031
Date of Original Submission:	June 26, 2013
Brand Name:	Isentress®
Generic Name:	Raltegravir
Strength and Formulation: **Sponsor:** **Indication:** **Submission Type:**	100 mg granules for suspension Merck Sharp & Dohme Corp. Treatment of HIV-1 infection in Children 4 weeks (b) (4) Supplemental NDA, Priority.
Pharmacometrics Team Leader	Jeffry Florian, Ph.D.
Clinical Pharmacology Team Leader	Islam Younis, Ph.D.
OCP Division	Division of Clinical Pharmacology IV
OND Division	Division of Antiviral Products

Subsequent to the finalization of the Clinical Pharmacology Review for NDA 205786 by Dr. Fang Li, a timing clarification was noted with regards to the response to Question 2.2.3 on page 6. The original Clinical Pharmacology Review stated that:

> "The Office of Scientific Investigations (OSI) inspected the laboratory responsible for the bioanalysis of all plasma samples collected in this trial under NDA 203045 and supplement NDA 22145 (SDN 230) [see the clinical pharmacology review by Dr. Ayala]. Briefly, following an onsite inspection of the (b) (4) OSI reported the PK data were acceptable for FDA review. Thus, all PK data presented in the trial report are considered reliable, including data for the granules for suspension formulation."

On November 6th, 2012 when the Clinical Pharmacology Review was entered into DARRTS, we were aware the clinical and bioanalytical site inspections under this application (NDA205786) had been performed and that the inspection report was pending. However, the official review from OSI was not completed until November 14th, 2013 (see review by Dr. Xikui Chen). The conclusion of the OSI review was that the clinical and bioanalytical data from study IMPAACT P1066 were acceptable for review. As such, the conclusions of the original Clinical Pharmacology Review remain valid.

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/s/

JEFFRY FLORIAN
12/11/2013

ISLAM R YOUNIS
12/12/2013

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 205-786	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Dates:	6/27/13; 10/1/13; 10/21/13; 12/2/13		
Division:	DAVP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Merck	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	ISENTRESS® [(b) (4)] Suspension	**Date Assigned:**	6/28/13
Generic Name:	Raltegravir potassium	**Date of Review:**	12/9/13
Indication:	treatment of HIV-1 infection in combination with other anti-retroviral agents	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	Granules for Suspension/ 100 mg		
Route of Administration:	Oral		

SYNOPSIS:

This document is an Addendum to the Original Biopharmaceutics review by Dr. Kareen Riviere dated November 18, 2013 in DARRTS. In the Original review it was reported that an approval recommendation could not be given for NDA 205786 because the submission of essential information needed for the final determination on the acceptability of the drug release ("solubility") test and acceptance criterion was pending.

In an Information Request (IR) letter sent to the Applicant on October 11, 2013, the ONDQA Biopharmaceutics Team recommended that the Applicant include drug release ("solubility") testing in the specifications of the drug product, with the following acceptance criteria: NLT [(b) (4)] and NLT [(b) (4)] for batch release and on stability. It was also recommended that the drug release ("solubility") test be conducted with the proposed product once reconstituted after [(b) (4)] and a minimum of [(b) (4)] units per test.

In a submission dated December 2, 2013, the Applicant provided their response to the October 11th IR letter. The Applicant developed and added a drug release test to the drug product specification. The Applicant's proposed drug release acceptance criterion of NLT [(b) (4)] is not supported by the provided data. Therefore, The ONDQA Biopharmaceutics Team recommended the Applicant to implement an acceptance criterion of NLT [(b) (4)] [(b) (4)] for the drug release test of the product. In an email addressed to Ms. Katherine Schumann dated December 9, 2013, the Applicant agreed to revise the drug release acceptance criterion to NLT [(b) (4)]% at [(b) (4)] minutes.

RECOMMENDATION:

NDA 205786 for ISENTRESS® (raltegravir [(b) (4)]) [(b) (4)] Suspension is recommended for approval from a Biopharmaceutics standpoint.

The following drug release test and acceptance criterion are acceptable for batch release and stability testing:

- ***Drug Release Test:*** Reconstitute 3 sachets into a 50 mL [(b) (4)].
- ***Acceptance Criterion:*** NLT [(b) (4)].

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESMENT OF BIOPHARMACEUTICS INFORMATION

1. Drug Release Test Method

As recommended by FDA in the October 11, 2013 IR letter, the Applicant developed a test to measure the release of raltegravir after the reconstituting the proposed drug product in a volume of water corresponding to that used for patient dosing.

The proposed method consists of the following steps:

- Reconstitute 3 sachets into a 50 mL (b) (4).
- (b) (4)
-
-
-

(b) (4)

Reviewer's Assessment:
The proposed drug release test method is consistent with Biopharmaceutics' recommendation; therefore, it is acceptable.

2. Drug Release Acceptance Criterion

The Applicant has developed and added a test for drug release from Raltegravir (b) (4) Suspension by HPLC for addition to the specification.

The Applicant's proposed drug release acceptance criterion for release and stability is:

Acceptance Criterion
NLT (b) (4)% at (b) (4)minutes

The Applicant selected and tested representative batches used in clinical studies, used in Formal Stability Studies (FSS), and manufactured at the commercial scale at the commercial sites for the purpose of specification development. They tested samples stored at ambient conditions, 25°C/60% RH, 30°C/65% RH or 30°C/75% RH since the time of manufacture. The selected batches were tested (b) (4) .

(b) (4)

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/s/

KAREEN RIVIERE
12/09/2013

ANGELICA DORANTES
12/09/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-786	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	6/27/13; 10/1/13; 10/21/13		
Clinical Division:	DAVP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Merck	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	ISENTRESS®	**Date Assigned:**	6/28/13
Generic Name:	Raltegravir potassium	**Date of Review:**	11/18/13
Indication:	treatment of HIV-1 infection in combination with other anti-retroviral agents	**Type of Submission:** 505(b)(1) New Drug Application	
Formulation/strengths:	Granules for Suspension/ 100 mg		
Route of Administration:	Oral		

SUMMARY:

Submission: This submission is a 505(b)(1) New Drug Application for 100 mg raltegravir potassium (b) (4) suspension. The proposed indication is for the treatment of HIV-1 infection in combination with other anti-retroviral agents.

The to-be marketed formulation was evaluated in the pediatric pharmacokinetic, safety, and efficacy study in HIV-infected pediatric patients (IMPAACT Protocol 1066). Additionally, the to-be marketed formulation was investigated in BE Study P068.

This submission does not include a dissolution method development report or a proposed dissolution acceptance criterion because the Applicant states that a dissolution test is not needed for their proposed product.

Review: The Biopharmaceutics review focuses on the evaluation of information supporting the approval of the Applicant's proposal of not having a QC dissolution test for their proposed product.

RECOMMENDATION:

Based on the provided dissolution data, the Applicant's proposal of not having dissolution as a QC test for their drug product was adequately justified and deemed acceptable. However, the provided data showed that after reconstitution, only (b) (4) of drug substance is in solution within (b) (4) and data to demonstrate that the solubility of the drug is not affected over the drug product's shelf-life were no provided. Therefore, the ONDQA Biopharmaceutics Team recommended that the Applicant include solubility testing in the specifications of the drug product, with the following solubility acceptance criteria: NLT (b) (4) for batch release and on stability. It was also recommended that the solubility test be conducted with the proposed product once reconstituted after (b) (4) (b) (4) and a minimum of (b) (4) units per test.

Overall at this time of the review process, the submission of essential information needed for the final determination of the acceptability the solubility test and acceptance criterion is lacking. The Applicant has notified FDA that the additional information will be submitted by November 29, 2013. Therefore, from the Biopharmaceutics perspective, an approval recommendation cannot be given for this NDA at the present time.

However, it should be noted that after the data that are pending are submitted and reviewed, Biopharmaceutics will revise as appropriate their recommendation on the approvability of NDA 205786 for ISENTRESS® (raltegravir (b) (4)) (b) (4) Suspension.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The Applicant identified (b) (4) anhydrous forms of raltegravir (b) (4) and was used throughout raltegravir development and clinical studies. Solubility of (b) (4) is 70.79 mg/ml. Solubility` of (b) (4) in buffer or gastric fluid at physiological pH (between pH 2 to 7) is substantially lower than its solubility in (b) (4). Raltegravir is considered a Biopharmaceutical Classification System (BCS) class II compound (i.e. low solubility and high permeability). The chemical structure of the raltegravir (b) (4) potassium salt is shown in Figure 1.

(b) (4)

Drug Product

The composition of the proposed drug product is shown in Table 1.

Table 1. Composition of Raltegravir (b) (4) Suspension

Component	Quality Reference[§]	Function	Unit strength
			mg/sachet
Raltegravir† (free phenol)	In-house[%]	Active	108.6 (100)
Hydroxypropyl Cellulose (b) (4) (b) (4)	USP-NF or Ph. Eur. ¶	(b) (4)	(b) (4)
(b) (4) Ethylcellulose) (b) (4)	#		
	USP-NF or Ph. Eur.		
Sucralose (b) (4)	USP-NF or Ph. Eur.		
Mannitol	USP-NF or Ph. Eur.		
(b) (4)	1		
Natural Banana Flavor (b) (4) (b) (4)	2		
(b) (4)			
Crospovidone,	USP-NF or Ph. Eur.		
Microcrystalline cellulose (b) (4) and Carboxymethylcellulose sodium (b) (4)	USP-NF or Ph. Eur.		
Magnesium Stearate (b) (4)	USP-NF or Ph. Eur.		
	Total Net Fill Weight		(b) (4)

The proposed product is provided as granules in an (b) (4) sachet. To prepare the suspension for dosing, the granules are mixed with 5 mL of water to prepare a 20 mg/ml suspension in a mixing cup. A dosing syringe is utilized to measure and administer the appropriate, weight based dose to the child.

2. Dissolution Method and Acceptance Criterion

The Applicant does not propose to implement a dissolution test for their proposed product. Their rationale is that when 100 mg strength product is constituted with 5 mL of water it achieves a concentration of 20 mg/mL, which is

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/s/

KAREEN RIVIERE
11/18/2013

ANGELICA DORANTES
11/18/2013

OFFICE OF CLINICAL PHARMACOLOGY
CLINICAL PHARMACOLOGY REVIEW

NDA#	205786, 203045 S-009, 22145 S-031
Date of Original Submission:	June 26, 2013
Brand Name:	Isentress®
Generic Name:	Raltegravir
Strength and Formulation: **Sponsor:** **Indication:** **Submission Type:**	100 mg granules for suspension Merck Sharp & Dohme Corp. Treatment of HIV-1 infection in Children 4 weeks (b) (4) (b) (4). Supplemental NDA, Priority.
Clinical Pharmacology/Pharmacometrics Reviewer	Fang Li, Ph.D.
Pharmacometrics Team Leader	Jeffry Florian, Ph.D.
Clinical Pharmacology Team Leader	Islam Younis, Ph.D.
OCP Division	Division of Clinical Pharmacology IV
OND Division	Division of Antiviral Products

Table of Contents

EXECUTIVE SUMMARY

Raltegravir (Isentress, MK-0518) oral tablets and chewable tablets have previously been approved by FDA for use in combination with an antiretroviral background therapy for the treatment of HIV-1 infection in adults (NDA22145) and in children and adolescents 2 to 18 years age (NDA203045). In this application, the sponsor is seeking approval for expanded pediatric use of raltegravir in younger HIV-infected children 4 weeks (b) (4) (b) (4) using a new formulation, raltegravir granules for suspension (GFS).

The application consisted of a previously reviewed Phase I bioequivalent study (Trial P068)) that compared the PK profile of raltegravir in adults, following the administration of GFS relative to the administration of tablets and chewable tablets, and a single Phase I/II, multicenter, open-label, noncomparative study (Trial IMPAACT P1066/Merck Protocol P022) which evaluated the safety, tolerability, pharmacokinetics, and antiretroviral activity of raltegravir in HIV-1 infected children and adolescents. A total of 152 infants, children and adolescents were enrolled and treated, among which, 26 patients (ages 4 weeks to < 2 years) were treated using raltegravir GFS formulation. A population PK study characterizing the PK of chewable tablets and GFS was also submitted.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted and agrees that it supports the use of raltegravir granules for suspension in pediatrics 4 weeks (b) (4) for the treatment of HIV-1 infection. These recommendations are contingent upon the pending agreement between the Agency and the sponsor on labeling changes.

The sponsor proposed the following dose regimen for pediatric patients 4 weeks (b) (4) (b) (4) administered the GFS.

Table 1: Proposed Dose for Isentress (b) (4) Suspension in Pediatric Patients 4 Weeks (b) (4)

Body Weight (kg)	Dose	Volume of Suspension to be Administered
(b) (4)		

*The weight-based dosing recommendation for (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily.

A simplified dosing table was recommended by the Office in order to reduce the complexity of the originally proposed doses which included narrow weight-bands and assessments to a tenth of a kilogram. The updated dosing results in similar exposures (C_{min} and AUC) to those originally proposed by the sponsor.

Table 2: FDA Recommended Dose for Isentress (b) (4) Suspension in Pediatric Patients 4 Weeks (b) (4)

Body Weight (kg)	Dose	Volume of Suspension to be Administered
3 to less than 4	20 mg twice daily	1 mL twice daily
4 to less than 6	30 mg twice daily	1.5 mL twice daily
6 to less than 8	40 mg twice daily	2 mL twice daily
8 to less than 11	60 mg twice daily	3 mL twice daily
11 to less than 14	80 mg twice daily	4 mL twice daily
14 to less than 20	100 mg twice daily	5 mL twice daily

*The weight-based dosing recommendation for (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily.

1.2 Post Marketing Commitments or Requirements

None

1.3 Summary of Key Clinical Pharmacology and Biopharmaceutics Findings

1. In study P068, which was partially reviewed under NDA 203045 and supplement NDA 22145 (SDN 230), the GFS formulation in adult healthy volunteers demonstrated increased bioavailability and rapid absorption compared to the adult poloxamer formulation and the pediatric chewable tablet formulation. In addition, the GFS formulation demonstrated a 4-folder increase in AUC and 2-fold increase in C_{max} compared to adult tablets. As such, the raltegravir GFS formulation was not bioequivalent with the previously approved adult tablets or chewable tablets for children. The reviewer concurs with the sponsor that the three formulations should not be used interchangeably. The label has been amended to reflect these observations accordingly [see General Dosing Recommendations on Label (2.1)].

2. In Study P022, raltegravir administered with an antiretroviral background therapy for the treatment of HIV-1 significantly decreased viral load after 24-week treatment (Figure 2). However, the virologic success rate, defined as less than 50 HIV-1 RNA copies/mL after 24 weeks, was 46.2% in patients 6 months to 2 years old (Cohort IV) and 38% in patients 4 weeks to 6 months of age (Cohort V). This was slightly lower than virologic success rate observed in children and adolescence 2 to 18 years old (50% to 60%) and can attributed to a higher baseline viral load in pediatrics 4 weeks to < 2 years of age compared to other pediatric groups and adults. As a result, these pediatrics may require longer

treatment duration (e.g. > 24 weeks) to suppress viral load to < 50 HIV-1 RNA copies /mL.

In previous trials in adults, adverse events that occurred at a higher frequency in raltegravir-treated subjects included severe rash, hypersensitivity reactions, and creatine kinase elevations. However, no relationship was identified between raltegravir exposure and these adverse events in adults. In study P022, pediatric patients administered GFS (Cohorts IV and V) had comparable AUC_{12}, C_{min}, but significantly higher C_{max} in comparison with those administered adult tablets and chewable tablets (Cohort I to III). Similar to the adult findings, the clinical pharmacology reviewer was not able to identify any relationships between raltegravir exposure and safety events in the current submission based on the available pediatric data.

1.4 Labeling Recommendations

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

- **4 weeks (b) (4):**
  - (b) (4) suspension: weight based- to maximum of 100 mg- twice daily, as specified in Table 2.

Table 2: Recommended Dose* for ISENTRESS (b) (4) Suspension in Pediatric Patients 4 weeks (b) (4)

Body Weight (kg)	Dose	Volume of Suspension to be Administered
3 (b) (4) to less than (b) (4) ~~4~~	20 mg twice daily	1 mL twice daily
(b) (4)		
4 (b) (4) to less than 6 (b) (4)	30 mg twice daily	1.5 mL twice daily
6 (b) (4) to less than (b) (4) ~~8~~	40 mg twice daily	2 mL twice daily
(b) (4)		
~~8~~ (b) (4) to less than 11 (b) (4)	60 mg twice daily	3 mL twice daily
11 (b) (4) o less than 14 (b) (4)	80 mg twice daily	4 mL twice daily
14 (b) (4) to less than 20 (b) (4)	100 mg twice daily	5 mL twice daily

*The weight-based dosing recommendation for (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily.

2 QUESTION-BASED REVIEW (QBR)

2.1 General Attributes

2.1.1 What are the proposed dosage form and route of administration?

Raltegravir is available in 400 mg film-coated tablets, 25 mg and 100 mg chewable tablets or 100 mg granules for suspension. It is used in combination with other antiretroviral agents.

The medications used in the current submission were granules for suspension, administered orally to pediatric patients who were 4 weeks to less than 2 years of age. Dosing was weight-based up to a maximum dose of 100 mg, twice daily. Raltegravir granules for suspension can be administered with or without food. Proposed pediatric dosing of granules for suspension from the sponsor and the Office can be found above in Table 1 and Table 2, respectively.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted two studies (P068 and Merck P022) to support dosing claims

Study P068 is a single-dose, open label, 4-period, randomized, crossover study in healthy adults subjects study to compare the pharmacokinetics of three formulations of raltegravir (FMI poloxamer tablet, chewable tablet, and granules for suspension) and evaluate the effect of food on the pharmacokinetics of chewable tablets.

Study IMPAACT P1066/Merck P022 is a Phase I/II, multicenter, open-label, noncomparative study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to evaluate the safety, tolerability, pharmacokinetics, and antiretroviral activity of raltegravir in HIV-1 infected children and adolescents ages 4 weeks to < 19 years of age. Raltegravir is administered in this study as the adult tablet, chewable tablet, and granules for suspension (GFS) in water. There are six Cohorts in this study. Raltegravir was administered as follows:

- Cohort I: ≥12 to < 19 years of age received adult tablets
- Cohort IIA: ≥6 to < 12 years of age received adult tablets
- Cohort IIB: ≥6 to < 12 years of age received chewable tablets
- Cohort IV: ≥ 6 months (defined as 180 days) to < 2 years of age received GFS
- Cohort V: ≥4 weeks (defined as 30 days) to < 6 months of age received GFS

The study consisted of two sequential Stages I and II. Stage I examined the pharmacokinetics, short-term tolerability, and safety or raltegravir in a limited number of patients to permit dose selection for further study in Stage II. In Cohort V, raltegravir was initiated simultaneously with a new background regimen at study entry. Subjects in Cohort IV had either raltegravir added to a stable background antiretroviral (ARV) regimen which was then optimized or followed the approach outlined for Cohort V. Once

the full cohort was enrolled, PK and short-term safety were again assessed, and if acceptable, then the full cohort passed the PK and safety criteria and a final recommendation of the raltegravir dose for further study during Stage II was provided.

The duration of treatment in Stage I was at least 48 weeks. The duration of chronic dosing treatment in Stage II was 48 weeks on the Stage I-selected dose. Patients in Stage II started raltegravir with an optimized background ARV regimen.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4 cell count are accepted markers for efficacy in trials with antiretroviral agents for the treatment of HIV-1 infection. The efficacy endpoints in study Merck P022 included the proportion of patients achieving < 50 HIV-1 RNA copies/mL, <400 HIV-1 copies/mL, or ≥ 1 $\log_{10}$ drop at Week 24 and Week 48. Other endpoints included $\log_{10}$ change from baseline in HIV RNA and change from baseline in absolute CD4 cell count and CD4 cell percentage.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

Yes, appropriate moieties were quantified in the two submitted clinical studies. The analytical method for the determination of raltegravir in human plasma involves isolation, via (b) (4) liquid extraction of the analyte and internal standard from plasma, followed by HPLC-MS/MS analysis. Two validated procedures were used to support this study, one with a linear calibration range of 1 to 3000 ng/mL, and the other with a linear calibration range of 10 to 10,000 ng/mL.

The Office of Scientific Investigations (OSI) inspected the laboratory responsible for the bioanalysis of all plasma samples collected in this trial under NDA 203045 and supplement NDA 22145 (SDN 230) [see the clinical pharmacology review by Dr. Ayala]. Briefly, following an onsite inspection of the (b) (4) OSI reported the PK data were acceptable for FDA review. Thus, all PK data presented in the trial report are considered reliable, including data for the granules for suspension formulation.

2.2.4 What are the characteristics of the exposure-response relationships for efficacy?

Relationships between PK parameters (such as AUC_{12}, C_{12hr}, C_{all}) and antiretroviral responses were explored by the sponsor using a logistic regression analysis. No statistically significant relationships were established between PK parameters and efficacy measures in analyses utilizing only patients from Cohorts IV and V. The lack of a significant relationship between PK parameters and efficacy endpoints suggests that the concentration ranges in Cohorts IV and V are at the top of the exposure-response curve.

This conclusion is further supported by the PK/PD analysis conducted by the sponsor. Briefly, a PK/PD viral dynamics model analysis was conducted by the sponsor and identified a sigmoid E_{max} relationship between Equivalent Constant Concentration (ECC)

and percent of viral inhibition. In this analysis, the sponsor defined an ECC based as the average percentage of viral inhibition achieved for a given raltegravir dose and dosing interval. The calculated ECC of patients 4 week to 2 years of age was predicted to be similar to the predicted viral inhibition achieved in adults administered raltegravir 400 mg BID. The detailed analysis can be referred in the appended Pharmacometric Review.

2.2.5 What are the characteristics of the exposure-response relationships for safety?

In previous trials in adults, the most common AEs (>10%) associated with using raltegravir were diarrhea, nausea, and headache. Adverse events that occurred at a higher frequency in raltegravir-treated subjects included: hypersensitivity reactions, rash, and creatine kinase elevations. In the original adult and previous pediatric raltegravir reviews, no relationships were identified between raltegraivr exposure and major adverse events of concern.

In pediatric patients 4 weeks to 2 years of age from the current submission, there were no short-term safety findings that led to rejection or modification of dose; Over 48-weeks of treatment, there was a single episode of allergic rash on Day 7 which caused treatment discontinuation. Overall, raltegravir exposure (AUC_{12} and C_{12hr}) were similar in pediatrics 4 weeks to < 2 years of age compared to pediatrics 2 to 18 years and adults. C_{max} was higher. However, we were not able to identify any relationships between raltegravir exposure and safety events based on the available pediatric data.

2.3 Additional Questions

2.3.1 Can the granule for suspension (GFS) formulation be used interchangeably with adult tablets or chewable tablets already approved for children 2 to < 18 years of age?

No. The granules for suspension (GFS) formulation used in children 4 weeks (b) (4) should not be used interchangeably with the adult tablets or chewable tablets approved for children 2 to < 18 years of age. The GFS formulation administered in healthy adults demonstrated more rapid absorption than adult tablets and chewable tablets, with significantly increased exposure (AUC and C_{max}) observed for the same dose of raltegravir. As a result of this observation, the clinical pharmacology review team recommended to include labeling language that the GFS formulation should not be used interchangeably with either the adult tablet of chewable tablet formulation [see General Dosing Recommendations on Label 2.1].

The sponsor conducted a Phase I study to compare the PK properties of three formulations in healthy adult volunteers. In the study, twelve subjects were randomized in a balanced, crossover design to receive 400 mg oral dose of: i) GFS; ii) adult tablets; iii) chewable tablets; or iv) chewable tablets following a high fat meal to assess food effect. The plasma concentration profile of raltegravir was measured over 72 hours following dosing.

Table 3 summarized the PK parameters of four treatments. The geometric mean (GM) AUC and C_{max} of raltegravir after administration of GFS were found to be 2.6-fold and 4.6-fold that of adult tablets, and 1.5-fold and 1.4-fold that of the chewable tablets,

respectively. The GFS formulation demonstrated faster absorption than adult tablets with a T_{max} of 1 hour versus 4 hours. In contrast, the T_{max} of GFS is similar to that observed for the chewable tablets (1 hour versus 0.5 hours). All three formulations had a similar terminal half-life of about 9~10 hours, suggesting raltegravir clearance was not affected by dosage formulation.

Table 3: Summary of PK Parameters Following a Single Dose of 400 mg Raltegravir GFS, Adult Tablet, and Chewable Tablet in Healthy Adult Subjects

PK parameters		i) GFS (fasted)	ii)Adult tablet (fasted)	iii)Chewable tablet (fasted)	iv)Chewable tablet with high fat meal
	N	GM	GM	GM	GM
$AUC_{0-\infty}$ (μM·hr)	12	50.4	19.2	34.2	32.3
C_{12hr} (nM)	12	162	149	134	387
C_{max} (nM)	12	23.2	5.0	16.1	6.14
T_{max} (hour)	12	1.0	4.0	0.5	1.0
$t_{1/2}$ (hour)	12	10	9.0	9.3	9.2

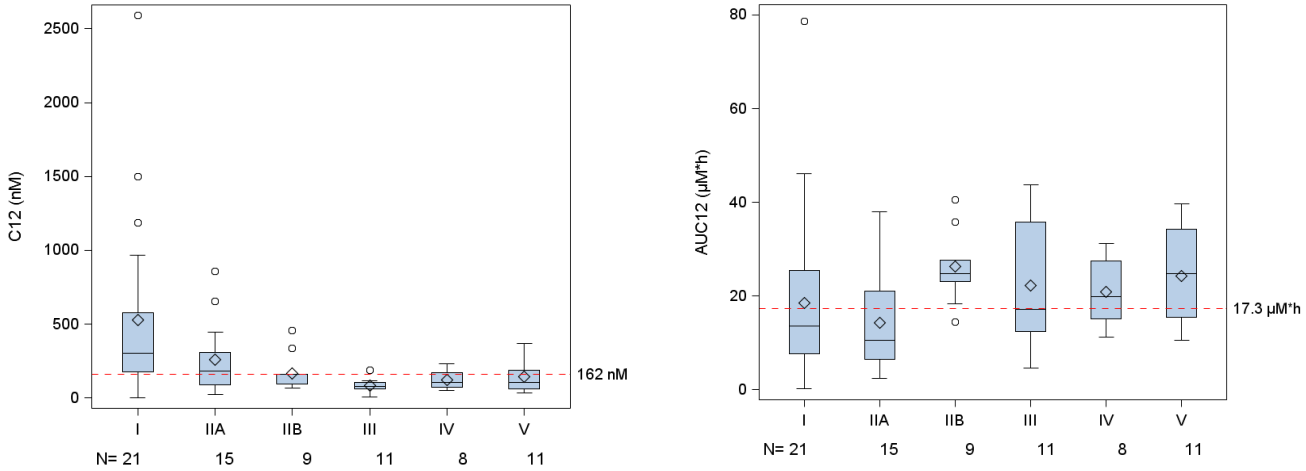
2.3.2 Does the proposed dosing regimen in children 4 weeks (b) (4) achieve similar exposure to that of pediatric patients 2 to 18 years of age and adults receiving approved raltegravir doses?

Yes, except for higher C_{max}, the observed raltegravir exposure (AUC_{12} and C_{12hr}) children of 4 weeks (b) (4) administered the granules for suspension formulation was similar to adults and adolescence administered raltegravir doses approved for those populations.

In the single pivotal study to support this pediatric application, the sponsor compared the PK parameters and virologic success rate in five cohorts. As shown in Figure 1 and Table 4, the mean AUC_{12} values in children 4 weeks to 2 years old (Cohorts IV and V: 20.9 and 24.2 μM·hr, respectively) were similar to those observed in children 6 to 12 years administrating chewable tablets (Cohort IIB) or children 2 to 6 years old (Cohort III). Those values were higher than those achieved in patients 6 to 12 years (Cohort IIB) and 12 to 18 years administrating adult tablets (Cohort I). The arithmetic mean AUC_{12} values in the youngest population were even higher than the achieved by adults administered 400 mg BID (17.3 μM·hr).

The mean C_{tr} concentrations 12 hours after dosing in children 4 weeks to 2 years (Cohorts IV and V: 122.3 and 144.3 nM, respectively) were lower than those in patients 6 to 18 years old (Cohort I and IIA and IIB), but they were higher than those achieved in patients in Cohort III, and in line with the adult geometric mean C_{12hr} of 161 nM after raltegravir 400 mg BID.

Figure 1: AUC_{12} and C_{12hr} by Cohorts after Administration of Proposed Raltegravir Dosing Regimen



- *The red reference line are adult geometric mean values following multiple dose of raltegravir tablets 400 mg BID*

Table 4: Comparison of Arithmetic Mean Raltegravir Exposure (AUC_{12} and C_{12hr}) and in Pediatric Patients Following Administration of Proposed Dosing Regimen

Cohort (ages):	I (12y to 18y)	IIA (6y to 12y)	IIB (6y to 12y, 6mg/kg)	III (2y to 6y) 6 mg/kg	IV (6m to 2y) 6 mg/kg	V (4wk-6m) 6 mg/kg	Adult 400 mg BID
N	21	15	9	11	8	11	6
AUC_{12} (µM*hr)	18.5	14.2	26.3	22.2	20.9	24.2	17.3
C_{12hr} (nM)	527.8	260.8	162.7	84.0	122.3	144.3	161.6
C_{max} (µM)	5.67	4.87	13.8	12.1	12.8	9.67	6.2

2.3.3 Does the proposed dosing regimen in children 4 weeks (b) (4) achieve similar efficacy to that of elder pediatric subjects receiving approved dosing regimen?

The observed data from Cohorts IV and V demonstrated a lower percentage of subjects with HIV RNA < 50 copies/mL at week 24 compared to that observed in previous pediatric cohorts and adults (Table 5). In contrast, the percentage of pediatrics in Cohorts IV and V with HIV RNA < 400 copies/mL at week 24 was similar to other pediatric cohorts and adult treatment-experienced subjects. This observation is partially explained

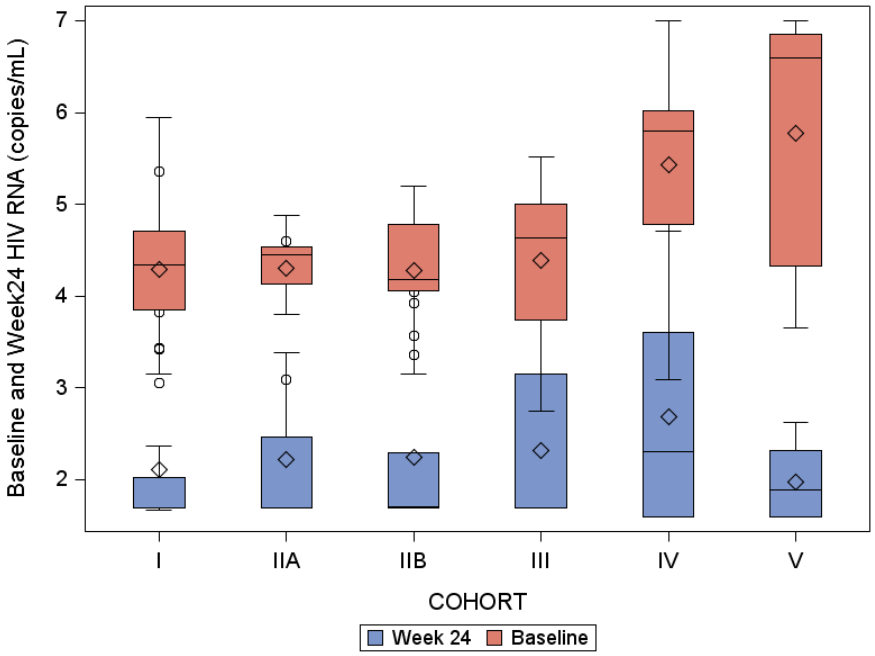
by the higher baseline viral load in Cohorts IV and V which may require longer treatment duration (>24 weeks) to suppress HIV virus to < 50 copies /mL.

Table 5: Comparison of Antiretroviral Response in Pediatric Patients Following Administration of Proposed Dosing Regimen

Cohort (Ages)	I (12y to 18y)	IIA (6y to 12y)	IIB (6y to 12y, 6mg/kg)	III (2y to 6y) 6 mg/kg	IV (6m to 2y) 6 mg/kg	V (4wk-6m) 6 mg/kg	Adults at 96 weeks 400 mg BID
HIV-1 RNA< 50 at Week24	39/57 (68.4%)	9/13 (69.2%)	9/18 (50%)	11/19 (57.9)	6/15 (40%)	3/8 (37.5%)	254/462 (55%)
HIV-1 RNA < 400 at Week24	48/57 (84.2%)	10/13 (76.9%)	14/18 (77.8%)	13/19 (68.4%)	8/15 (53.3%)	6/8 (75%)	-
HIV-1 RNA< 400 or 1 Log_{10} Drop	54/57 (94.7%)	13/13 (100%)	17/18 (94.%)	18/19 (94.7%)	10/15 (66.7%)	6/8 (75%)	-

As shown in Table 5, the observed 24-week virologic success rate (measured as <50 HIV RNA copies/ml) in children 4 weeks to 2 years old was observed slightly lower than that in older children (<40% versus >50%). The reviewer explored explanations for this observed lower response in Cohorts IV and V and identified these cohorts had higher baseline viral load compared to adults or pediatrics in other cohorts (Figure 2).This is further supported by the similar response between pediatric cohorts and adults at week 24 based on a virologic response criteria of < 400 HIV RNA copies/mL. Additional evidence of effectiveness of the proposed pediatric regimen comes from the virologic time course in Cohorts IV and V. Viral load continued dropping in some patients beyond 24 weeks. At week 48, more patients in Cohorts IV and V reached virologic success (HIV RNA < 50 copies/mL). Overall, it was concluded that the lower antiretroviral response based on HIV RNA < 50 copies/mL at week 24 in patients 4 weeks to less than 2 years of age was due to higher baseline viral load and that these patients in Cohorts IV and V needed a longer treatment in order to achieve the target of HIV RNA < 50 copies/mL.

Figure 2: Log_{10} HIV-1 RNA Copies /mL at Baseline (red) and Week 24 (blue)

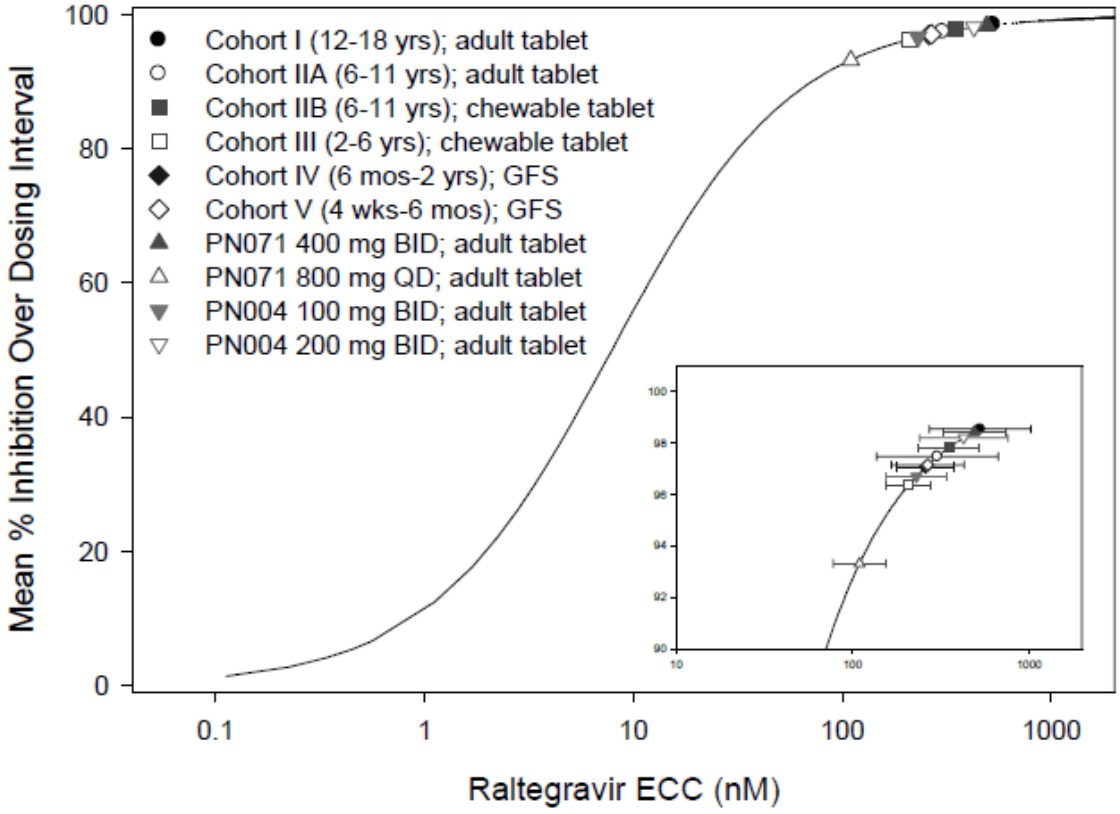


2.3.4 Is there any evidence of an exposure-response efficacy relationship for raltegravir? Does the exposure-response efficacy relationship for raltegravir support the proposed raltegravir doses in children age 4 weeks (b) (4) (b) (4) ?

Yes, an exposure-response (ER) relationship exists between raltegravir equivalent constant concentration (ECC) and percent of viral inhibition. Based on a PK/PD viral dynamic model developed by the sponsor, a sigmoid E_{max} model was constructed that characterizes the relationship between viral inhibition and raltegravir ECC (Figure 3). ECC is calculated as the average viral inhibition obtained based on the full raltegravir PK profile, accounting for both dose and dosing interval. A detailed description of the method used for calculated ECC is depicted in Figure 10.

The calculated ECC value for patients 4 weeks to 2 years of age (Cohorts IV and V) was similar to that calculated for adults administered raltegravir tablets 400 mg BID. Based on this observation and the observed PK exposures for raltegravir described in Question 2.3.2, raltegravir exposure and the raltegravir ECC achieved in children 4 weeks to 2 years of age appears adequate. In addition, the observed raltegravir exposures and ECC is higher than that observed in adult patients administered raltegravir 800 mg QD, which did not achieve non-inferiority compared to the approved 400 mg BID adult regimen. Pediatric patients in cohort I to III was also found to have similar exposure and viral inhibition as those observed in adults with raltegravir 400 mg BID dose.

Figure 3: Geometric Mean ECC and Percent Inhibition over the Dosing Interval for IMPAACT Protocol 1066 and Merck Protocol 071 (Insert error bars represent 95% confidence interval of ECC values)



Source: Figure 11-11 on Page 168 of Study Report P022v1

2.3.5 Are there any identified safety issues or exposure-response safety relationships in pediatric patients 4 weeks to 2 years old administered the raltegravir GFS formulation?

Administration of the GFS formulation in patients 4 weeks to 2 years of age resulted in higher C_{max} than observed in pediatrics 2 to 18 years and adults; however, the impact of this increase in C_{max} on safety could not be determined from the available data in Cohorts IV and V. A summary of the safety events observed in Cohorts IV and V can be found in Table 12-3 of the clinical study report for study P022v1.

2.3.6 Are there proposed raltegravir doses in pediatric patients 4 weeks (b) (4) administered the raltegravir GFS formulation acceptable?

The sponsor proposed raltegravir dosing table (Table 1) for children 4 weeks (b) (4) (b) (4) included (b) (4) dosing groups, and targeted a raltegravir dose of 6 mg/kg. The body weight interval within some of these groups was as narrow as <1 kg. Given the relative rapid change in body weight for pediatrics at this stage of development, the reviewer recommended a simplified raltegravir dosing regimen as shown in Table 2.

The new dosing regimen maintains the original pediatric dosing target of 6 mg/kg but permitted raltegravir mg/kg dosing to range between 4.8-7.5 mg/kg rather than (b) (4) as was maintained with the sponsor's dosing table. In addition, the proposed dosing regimen reduces the originally proposed (b) (4) dosing categories to six dosing categories. Only pediatric patients with body weights between 3.7-4.5 kg, 7.6-9.0 kg, and 11-11.4 kg will have altered dosing with the FDA's proposed dosing compared to that proposed by the sponsor. Of these pediatrics, only patients with body weight 3.7-3.9 kg and 7.6-7.9 kg will receive a reduced dose compared to that proposed by the sponsor, and this reduction in dose is not expected to appreciably impact efficacy. These proposed dosing changes are tabulated and illustrated graphically in the Pharmacometrics Review.

3 APPENDICES

3.1 Individual Study Review

3.1.1 Study P068

PK profile of the GFS formulation (study P068) in comparison with the approved dosage forms

In study P068, the sponsor evaluated raltegravir PK properties for the GFS formulation in healthy adult subjects following a single dose of raltegravir and compared these observations with raltegravir PK for the adult poloxamer tablets and chewable tablets. In addition, the sponsor studied the effect of a high fat meal on the PK of the EC formulation (chewable tablets). Part of data in this study has previously been reviewed by Dr. Ruben Ayala in the Office of Clinical Pharmacology of the Agency, under NDA203045 (raltegravir ethylcellulose chewable tablet) and sNDA 22145 (SDN 230) (raltegravir poloxamer adult tablet). Please refer his report for details.

In all, twelve (12) subjects received 4 treatments (Treatment A, B, C, and D) randomized in a balanced, crossover design in Periods 1 through 4. There was a minimum of 4 days of washout between the single doses in each treatment period. Treatments A through D were as follows:

- Treatment A: 400 mg MK-0518, poloxamer (administered fasted, adult tablets)
- Treatment B: 400 mg MK-0518, EC (administered fasted, chewable tablets)
- Treatment C: 400 mg MK-0518, OG in a liquid suspension (administered fasted, GFS)
- Treatment D: 400 mg MK-0518, EC (administered with a high-fat meal, chewable tablets)

The PK parameters of GFS and other formulations were summarized in Table 6 and visually plotted in Figure 4. The results of this study were previously reviewed in the Clinical Pharmacology Review by Dr. Ruben Ayala under NDA 203045 and supplement NDA 22145 (SDN 23). The previous review did not comment on the results of the OG formulation (referred to as the GFS formulation earlier in this review) as no efficacy data with that formulation was available. The current review expands upon the observations

from the original review with details on how the OG formulation compares to the raltegravir adult tablet and chewable tablet formulations.

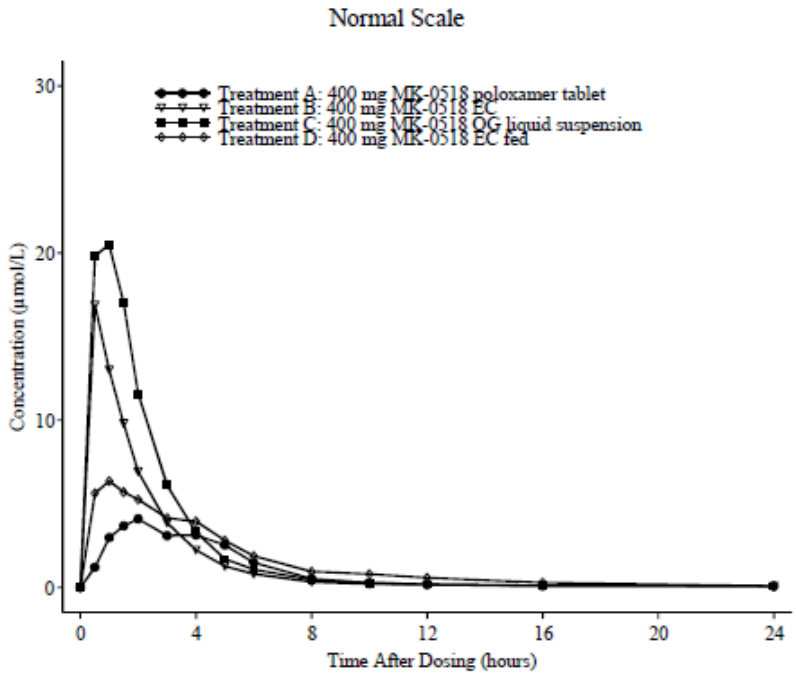
Table 6: Summary of Plasma PK Following Single-Dose Administration of MK-518 OG Formulation, Poloxamer Tablet and EC Tablet in Healthy Adult Volunteers

Pharmacokinetic Parameter (Units)	N	Treatment A† GM	Treatment B† GM	Treatment C† GM	Treatment D† GM	Comparison	GMR (90% CI)	rMSE‡
C_{12hr} (nM)§	12	149	134	162	387	Treatment C/Treatment A	1.09 (0.84 , 1.41)	0.3794
						Treatment C/Treatment B	1.20 (0.92 , 1.56)	
						Treatment D/Treatment B	2.88 (2.21 , 3.75)	
						Treatment B/Treatment A	0.90 (0.70 , 1.18)	
$AUC_{0-\infty}$ (µM•hr)§	12	19.2	34.2	50.4	32.3	Treatment C/Treatment A	2.62 (2.17 , 3.17)	0.2748
						Treatment C/Treatment B	1.47 (1.22 , 1.78)	
						Treatment D/Treatment B	0.94 (0.78 , 1.14)	
						Treatment B/Treatment A	1.78 (1.47 , 2.15)	
C_{max} (µM)§	12	5.00	16.1	23.2	6.14	Treatment C/Treatment A	4.64 (3.41 , 6.30)	0.4425
						Treatment C/Treatment B	1.44 (1.06 , 1.95)	
						Treatment D/Treatment B	0.38 (0.28 , 0.52)	
						Treatment B/Treatment A	3.22 (2.37 , 4.38)	
T_{max} (hr)□	12	4.0	0.5	1.0	1.0			
$t_{1/2l}$ (hr)¶		1.5 (0.3)	1.7 (0.2)	1.6 (0.3)	2.0 (0.6)			
$t_{1/2T}$ (hr)¶	12	9.0 (5.9)	9.3 (5.1)	10.0 (3.2)	9.2 (3.8)			

† Treatment A = 400 mg MK-0518, poloxamer (administered fasted).
Treatment B = 400 mg MK-0518, EC (administered fasted).
Treatment C = 400 mg MK-0518, OG in a liquid suspension (administered fasted).
Treatment D = 400 mg MK-0518, EC (administered with a high-fat meal).
‡ rMSE: Root mean square error on natural log-scale. When multiplied by 100, it provides an estimate of the pooled within-subject coefficient of variation.
§ Back-transformed least squares mean and confidence interval from mixed effects model performed on the natural log-transformed values.
□ Median values presented for T_{max}.
¶ Harmonic mean (jack-knife standard deviation) values presented for $t_{1/2l}$ and $t_{1/2T}$. For $t_{1/2l}$, the N's for Treatments A, B, C, and D are 11, 12, 12, and 10, respectively.

Source: Table 11-1 on page 40 of sponsor's clinical report P068

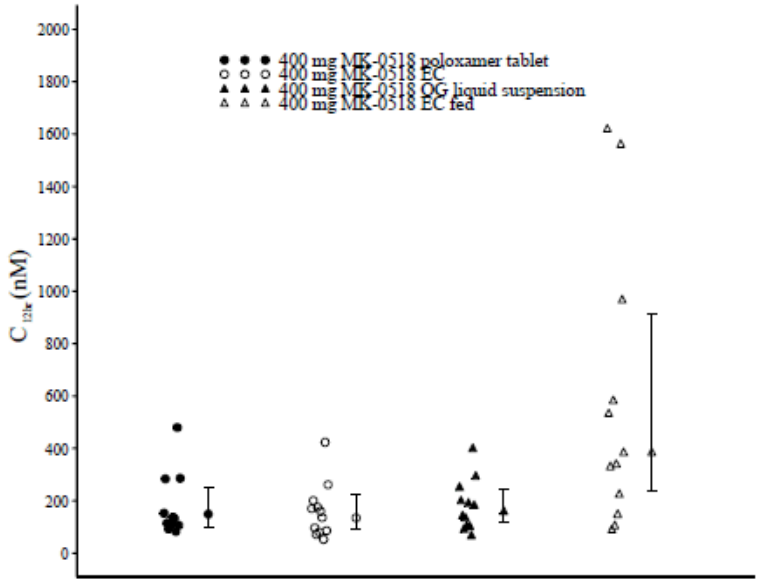
Figure 4: Mean Plasma Concentration-Time Profiles for MK-0518 Following Single-Dose Administration of the MK-0518 OG Formulation, the MK-0518 Poloxamer Formulation, and the MK-0518 EC Formulation in Healthy Adult Subjects (N=12)



Source: Figure 11-1 on page 39 of sponsor's clinical report P068

Raltegravir concentration after 12 hours (C_{12hr}) post dose was compared among the three formulations (Figure 5). The geometric means of MK-0518 C_{12hr} of the OG formulation was found to be statistically different from the adult poloxamer tablet or the chewable tablet. The C_{12hr} geometric mean ratio (GMR) for OG/FMI poloxamer (Treatment A/C) was 1.09 with a corresponding 90% CI of (0.84, 1.41). The C_{12hr} GMR of OG/EC was 1.2 with a corresponding 90% CI of (0.92, 1.56). The AUC and C_{max} values for the OG formulation were also much higher than their corresponding geometric means for the EC or poloxamer tablets. Relative to the EC formulation, the $AUC_{0-\infty}$ and C_{max} GMRs and corresponding 90% CI were 1.47 (1.22, 1.78) and 1.44 (1.06, 1.95), respectively. Relative to the poloxamer formulation, $AUC_{0-\infty}$ and C_{max} respective GMRs and corresponding 90% CI were 2.62 (2.17, 3.17) and 4.64 (3.41, 6.30), respectively. The OG formulation has faster absorption than the adult tablets.

Figure 5: Individual C_{12hr} (nM) Values, Geometric Means, and 95% CI following Single-Dose Administration of 400 mg MK-0518 OG Formulation, Poloxamer Formulation and EC formulation in Healthy Adult Subjects (N=12)



Source: Figure 11-2 on page 43 of sponsor's clinical report P068

Reviewer's Comment: As demonstrated in Figure 4*, the three formulations demonstrated very different PK profiles and the OG formulation (granules for suspension; GFS) was determined not to be bioequivalent to the already approved adult poloxamer tablet and pediatric chewable tablet. Based on this observation, the label was changed to reflect that the use of the three dosage forms is not interchangeable.*

3.1.2 Study IPMACCT 068/Merck P022

Pharmacokinetics and Efficacy Study (Merck P022)

The sponsor submitted a single pivotal Phase I/II study (IMPAACT p1066, Merck protocol P022) study to evaluate the safety, tolerability, pharmacokinetics, and efficacy

of raltegravir in combination with an optimized background regimen in HIV-1 infected pediatric patients. The study is a 240-week, ongoing, multicenter, open-label, and non-comparative study including infants, children, and adolescents ages from 4 weeks to < 19 years of age. In the study, raltegravir were administered as adult tablets, chewable tablet, or granules for suspension (GFS). Patients were divided into six cohorts by age and formulation received:

- Cohort I: ≥12 to < 19 years of age received adult tablets
- Cohort IIA: ≥6 to < 12 years of age received adult tablets
- Cohort IIB: ≥6 to <12 years of age received chewable tablets
- Cohort III: ≥ 2 to <6 years of age received chewable tablets
- Cohort IV: ≥ 6 months (defined as 180 days) to < 2 years of age received GFS
- Cohort V:≥ 4 weeks (defined as 30 days) to < 6 months of age received GFS

The study included two sequential stages: I and II. Stage I examined the pharmacokinetics, short-term tolerability, and safety of raltegravir in patients to permit dose selection for further study in Stage II. Stage II was chronic treatment that last for 48 weeks on the Stage I selected dose. Upon completion of 48 weeks, raltegravir was available to patients via a protocol extension inclusive of 5 years from initial exposure to raltegravir (48 weeks of treatment plus 4 years follow-up, total duration of 240 weeks).

A total of 152 infants, children and adolescents were enrolled and treated in P1066, of which, 126 patients were in Cohorts I-III and 26 patients were in Cohorts IV and V. The disposition of patients in Cohorts IV and V were summarized in Table 7.

Part of the data (Cohort I to III) was evaluated by FDA in the first pediatric submission in support of dosing recommendation for children 2 to 18 years old. The primary focus of the sponsor's study report was the use of raltegravir in infants (b) (4) ≥ 4 weeks (b) (4) receiving the GFS formulation. In this review, the reviewer focused on analyses of pharmacokinetics and efficacy. Safety review can be referred in separate report by the medical reviewer.

Table 7: Overall Disposition of Patients by Cohort (IV and V, All Data as of 07-Feb-2013)

	Cohort IV (N=15) n (%)	Cohort V (N=12) n (%)	Total (N=27) n (%)
Total	15 (100)	12 (100)	27 (100)
Treated	14 (93.3)	12 (100)	26 (96.3)
Non-treated	1 (6.7)	0 (0)	1 (3.7)
Patients Completed Week 24[†]	14 (93.3)	9 (75)	23 (85.2)
Patients Completed Week 48[‡]	14 (93.3)	7 (58.3)	21 (77.8)
Off Study Drug	1 (6.7)	2 (16.7)	3 (11.1)
Died	1 (6.7)	0 (0)	1 (3.7)
Protocol Defined Toxicity	0 (0)	1 (8.3)	1 (3.7)
Not Able to Attend Clinic	0 (0)	1 (8.3)	1 (3.7)
Off Study	1 (6.7)	1 (8.3)	2 (7.4)
Death	1 (6.7)	0 (0)	1 (3.7)
Subject/parent not able to get to clinic	0 (0)	1 (8.3)	1 (3.7)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
[†] Patient was on study treatment to at least Rel Day 127.
[‡] Patient was on study treatment to at least Rel Day 295.

Source: Table 10-4 on page 114 of sponsor's report P022v1

PK Assessments:

The Primary objective for pharmacokinetics was to evaluate the steady state plasma concentration profiles and PK parameters of raltegravir in children and adolescents. For intensive PK evaluations of Stage I patients in Cohorts IV and V, blood samples were collected at the following time points: Cohort V, pre-dose, 0.5, 1, 2, 4, and 12 hours post dosing. Cohort V, pre-dose, 0.5, 1, 3-5, and 8-10 hours post dosing. Population PK sampling was performed for all patients in Stages I and II at Weeks 4, 8, 12, and 24. The primary analyses of pharmacokinetics included the calculation at pharmacokinetic parameters ($AUC_{0\text{-}12hr}$) and concentration at 12 hours post dose (C_{12hr}) using noncompartmental analysis. The PK target for Cohorts IV and V was to maintain a geometric mean raltegravir $AUC_{0\text{-}12\ hr}$ between 14 and 45 μM·hr and a geometric mean raltegravir C12 hr of greater than 75 nM.

The final selected dose of raltegravir for Cohorts IV and V, based on review of Stage I PK and short-term safety data, is weight-based dosing to approximate 6 mg/kg BID. Raltegravir PK parameters (geometric mean of AUC_{12} and C_{12hr}) in pediatric patients are summarized in Table 8.

Table 8: Summary of Raltegravir PK Parameters at Final Recommended Doses in IMPAACT Protocol 1066

Age	Cohort	Formulation	Final Recommended Dose	N†	Mean Weight (kg)	Mean Dose (mg)	Mean Dose (mg/kg)	Geometric Mean (%CV) $AUC_{0\text{-}12hr}$ (μM*hr)	Geometric Mean (%CV) C_{12hr} (nM)
12 to 18 years	I	Adult tablet	400 mg BID	11	43.55	390.91	9.28	15.71 (98)	332.63 (78)
6 to < 12 years	IIA	Adult tablet	400 mg BID, for patients weighing ≥25 kg	11	31.54	400.00	13.45	15.84 (120)	246.09 (221)
6 to < 12 years	IIB	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	10	36.36	230.00	6.47	22.58 (34)	129.60 (88)
2 to <6 years	III	Chewable tablet	6 mg/kg BID, maximum of 300 mg BID	12	14.24	89.58	6.24	17.95 (59)	71.16 (55)
6 months to <2 years	IV	Granules for Suspension	6 mg/kg BID	8	8.49	51.3	5.93	19.8 (34)	108.2 (52)
4 weeks to <6 months	V	Granules for Suspension	6 mg/kg BID	11	5.50	31.4	5.70	22.3 (40)	116.6 (68)

† Number of patients with intensive PK results at the final recommended dose.

Source: Table 11-13 on page 159 of sponsor's report P022v1

Reviewer's comment: No issues were identified in the reports on the bioanalytical method for quantifying raltegravir concentrations in collected blood samples. A Division of Scientific Investigation (DSI) inspection was arranged for inspecting two clinical sites in South Africa and one bioanalytical site at (b) (4) *Of the 27 enrolled patients in Cohorts IV and V, the majority (18, 66.7%) were enrolled in South Africa, The PK data from Cohorts IV and V (for patients 4 weeks to 2 years old) is pivotal for determining raltegravir doses for this pediatric age group. At this time, the result from the inspection is still pending.*

Efficacy Assessments:

The primary efficacy assessments included evaluation of the antiretroviral activity and immunological activity of raltegravir at Weeks 24 and 48 in combination with optimized background therapy (OBT). HIV RNA and CD4 cell count were determined at screening, entry, Weeks 4, 4, 8, 12, 24, 36, and 48, at a safety visit whose dose was increased to the Stage II dose, at the 14-day post therapy follow-up visit, and at an early discontinuation visit. The antiretroviral activity of raltegravir at weeks 24 and 48 was measured by the proportion of patients achieving HIV RNA below 400 copies /mL, or 1-log drop in HIV RNA from baseline, and to evaluate the immunological activity of raltegravir at the selected dose in combination with OBT, as measured by changes in CD4 cell count and CD4% over 24 and 48 weeks. Summary of antiretroviral response in pediatric 4 weeks to < 2 years of age after 24 and 48 weeks of treatment are shown in

Table 9 and Table 10, respectively. For purpose of comparison, summary of antiretroviral response in pediatric 2 to <19 years of age after 48 weeks of treatment is shown in Table 11.

Table 9: Summary of Efficacy Analysis by Cohort (IV and V) at Week 24 Non-Completer=Failure Approach

Parameter	Cohort IV (N=14)		Cohort V (N=8)		Total (N=22)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with >=1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL	12/14	85.7 (57.2, 98.2)	8/8	100 (63.1, 100)	20/22	90.9 (70.8, 98.9)
Proportion of patients with HIV RNA <50 copies/mL	6/13	46.2 (19.2, 74.9)	3/8	37.5 (8.5, 75.5)	9/21	42.9 (21.8, 66)
Proportion of patients with HIV RNA <400 copies/mL	8/14	57.1 (28.9, 82.3)	6/8	75 (34.9, 96.8)	14/22	63.6 (40.7, 82.8)
Proportion of patients with HIV RNA below the limit of quantification	6/14	42.9 (17.7, 71.1)	3/8	37.5 (8.5, 75.5)	9/22	40.9 (20.7, 63.6)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in plasma HIV RNA (log10copies/mL)	-2.8	(-3.6, -1.9)	-3.8	(-4.8, -2.8)	-3.1	(-3.8, -2.5)
Change from baseline in CD4 cell count (cells/mm3)	400.5	(60.3, 740.6)	662.1	(161.6, 1162.7)	500.1	(237.6, 762.6)
Change from baseline in CD4 percent	6.2	(1.3, 11.2)	9.7	(5.1, 14.2)	7.5	(4.2, 10.9)

N = Number of patients in each cohort.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of patients.
For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Approaches for handling missing data:
-For binary endpoints, Non-Completer=Failure approach was used such that missing values were considered as failures regardless of reason unless flanked by two successes, in which case patients were excluded.
-For continuous endpoints (e.g. change from baseline in CD4 cell counts and percent), Observed Failure approach was used such that baseline values were carried forward for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.

Data Source: [16.4.3.51; 16.4.3.9; 16.4.3.59]

Source: Table 14-14 on page 369 of sponsor's report P022v1

Table 10: Summary of Efficacy Analysis by Cohort (IV and V) at Week 48 Non-Completer=Failure Approach

Parameter	Cohort IV (N=14)		Cohort V (N=8)		Total (N=22)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with >=1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL	13/14	92.9 (66.1, 99.8)	4/7	57.1 (18.4, 90.1)	17/21	81 (58.1, 94.6)
Proportion of patients with HIV RNA <50 copies/mL	7/13	53.8 (25.1, 80.8)	3/7	42.9 (9.9, 81.6)	10/20	50 (27.2, 72.8)
Proportion of patients with HIV RNA <400 copies/mL	10/14	71.4 (41.9, 91.6)	4/7	57.1 (18.4, 90.1)	14/21	66.7 (43, 85.4)
Proportion of patients with HIV RNA below the limit of quantification	8/14	57.1 (28.9, 82.3)	3/7	42.9 (9.9, 81.6)	11/21	52.4 (29.8, 74.3)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in plasma HIV RNA (log10copies/mL)	-2.8	(-3.8, -1.7)	-2.6	(-5.2, 0)	-2.7	(-3.6, -1.8)
Change from baseline in CD4 cell count (cells/mm3)	278.8	(-185.6, 743.2)	989.5	(81.1, 1897.9)	492.0	(86.3, 897.7)
Change from baseline in CD4 percent	6.4	(1.4, 11.3)	11.1	(3.8, 18.4)	7.8	(3.9, 11.6)

N = Number of patients in each cohort.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of patients.
For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Approaches for handling missing data:
-For binary endpoints, Non-Completer=Failure approach was used such that missing values were considered as failures regardless of reason unless flanked by two successes, in which case patients were excluded.
-For continuous endpoints (e.g. change from baseline in CD4 cell counts and percent), Observed Failure approach was used such that baseline values were carried forward for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.

Data Source: [16.4.3.51; 16.4.3.9; 16.4.3.59]

Source: Table 14-15 on page 370 of sponsor's report P022v1

Table 11: Summary of Efficacy Analysis by Cohort (IV and V) at Week 48 Observed Failure Approach

Parameter	Cohort I (N=59)		Cohort IIA (N=4)		Cohort IIB (N=13)		Cohort III (N=20)		Total (N=96)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of patients with >=1 log10 drop from baseline in HIV RNA or HIV RNA <400 copies/mL	42/56	75 (61.6, 85.6)	3/4	75 (19.4, 99.4)	10/11	90.9 (58.7, 99.8)	17/20	85 (62.1, 96.8)	72/91	79.1 (69.3, 86.9)
Proportion of patients with HIV RNA <50 copies/mL	32/56	57.1 (43.2, 70.3)	2/4	50 (6.8, 93.2)	6/11	54.5 (23.4, 83.3)	12/20	60 (36.1, 80.9)	52/91	57.1 (46.3, 67.5)
Proportion of patients with HIV RNA <400 copies/mL	39/56	69.6 (55.9, 81.2)	2/4	50 (6.8, 93.2)	10/11	90.9 (58.7, 99.8)	16/20	80 (56.3, 94.3)	67/91	73.6 (63.3, 82.3)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	168.2	(117.5, 218.9)	189.5	(-154.2, 533.2)	76.8	(-85.3, 238.9)	158.1	(11.7, 304.4)	155.7	(108.3, 203.1)
Change from baseline in CD4 percent	5.2	(3.9, 6.6)	6.0	(-2.6, 14.6)	1.6	(-2.7, 5.9)	4.3	(1, 7.6)	4.6	(3.4, 5.8)

N = Number of patients in each cohort.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of patients.
For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Observed Failure Approach for handling missing data:
-For binary endpoints, missing values were considered as failures for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.
-For continuous endpoints (e.g. change from baseline in CD4 cell counts and percent), baseline values were carried forward for patients missing data due to discontinuation of study treatment for lack of efficacy or for non-treatment related reasons with last available HIV RNA value < 1 log10 drop from baseline and >=400 copies/mL; otherwise patients with missing values were excluded.

Data Source: [16.4.3.51; 16.4.3.9; 16.4.3.59]

Source: Table 14-19 on page 374 of sponsor's report P022v1

Safety Assessment

In Cohorts IV and V, there were no short-term safety findings that led to rejection or modification of dose; at weeks 24 and 48 of treatment. There was a single rash adverse event on Day 7 which caused treatment discontinuation. There were two Grade 3 or higher adverse events that were considered drug-related, and 7 serious adverse events, one of which was considered drug related. There was one event of gastroenteritis which resulted in death at week 60 on study and was determined to be not related to study therapy. Summary of adverse event in Cohorts IV and V by the sponsor are summarized in Table 12.

Table 12: Summary of Clinical Adverse Events by Cohort (V and V)

Summary of Clinical Adverse Events by Cohort (IV and V)
Weeks 0 – 24

	Cohort IV (N=14) n (%)	Cohort V (N=12) n (%)	Total (N=26) n (%)
With one or more clinical adverse events	14 (100)	12 (100)	26 (100)
With no clinical adverse event	0 (0)	0 (0)	0 (0)
With one or more serious clinical adverse events	5 (35.7)	2 (16.7)	7 (26.9)
With one or more serious drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	1 (8.3)	1 (3.8)
With one or more Grade 3 or greater clinical adverse events	3 (21.4)	2 (16.7)	5 (19.2)
With one or more Grade 3 or greater drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
Events were included if they occurred while on study drug or within 14 days after discontinuation of study drug.
*Drug related adverse events were determined by the investigator to be possibly, probably or definitely related to raltegravir.
Complete Week 24 data (Patient was on study treatment to at least Rel Day 127) is available for 75.0% (9/12) of Cohort V patients.

Summary of Clinical Adverse Events by Cohort (IV and V)
Weeks 0 – 48

	Cohort IV (N=14) n (%)	Cohort V (N=12) n (%)	Total (N=26) n (%)
With one or more clinical adverse events	14 (100)	12 (100)	26 (100)
With no clinical adverse event	0 (0)	0 (0)	0 (0)
With one or more serious clinical adverse events	6 (42.9)	2 (16.7)	8 (30.8)
With one or more serious drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	1 (8.3)	1 (3.8)
With one or more Grade 3 or greater clinical adverse events	4 (28.6)	2 (16.7)	6 (23.1)
With one or more Grade 3 or greater drug related* clinical adverse events	0 (0)	1 (8.3)	1 (3.8)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
Events were included if they occurred while on study drug or within 14 days after discontinuation of study drug.
*Drug related adverse events were determined by the investigator to be possibly, probably or definitely related to raltegravir.
Complete Week 48 data (Patient was on study treatment to at least Rel Day 295) is available for 58.3% (7/12) of Cohort V patients.

Source: Table 12-3 and 12-5 on page 190 and 192 of sponsor's report P022v1

3.2 Pharmacometric Review

1. Key Review Questions

The key Pharmacometric review questions can be found in section QBR 2.3 [Additional Questions]. Similarly, labeling comments and recommendations can be found in Section 1 of the review.

2. Pertinent Regulatory Background

Raltegravir (also known as ISENTRESS®, MK-0518) is a HIV integrase strand transfer inhibitor that is active against HIV-1 virus. Raltegravir as oral tablets was first approved (NDA 22-145) by FDA on October 12, 2007 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Subsequently, on December 21, 2011, ISENTRESS chewable tablets were approved for pediatric use in patients from 2 to 18 years of age.

This application is seeking approval for pediatric use of raltegravir in patients 4 weeks (b) (4) (b) (4) with a new formulation, raltegravir granules for suspension (GFS).

One pediatric study IMPAACP P1066/ Merck P022 was submitted to support efficacy, safety, and labeling revision proposed by the sponsor. The study is a 240-weeks ongoing study including patients from 4 weeks to 18 years of age. Data in pediatric patients from 2 to 18 years of age has previously been submitted and reviewed by FDA. The purpose of this application is to extend the current raltegravir indication to pediatrics 4 weeks (b) (4) (b) (4) (Cohorts IV and V) using GFS a formulation. At this time, Merck is not requesting pediatric exclusivity under the "Best Pharmaceuticals for Children Act of 2007".

3. Sponsor's Analysis

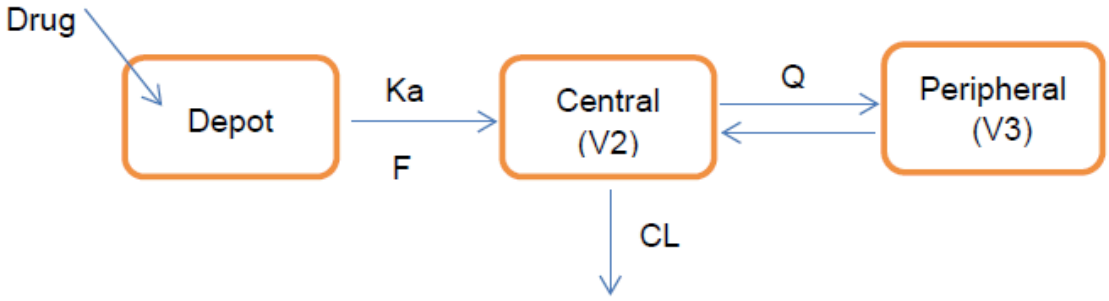
3.1 Population PK analysis

Objectives: The primary objectives of the population PK analyses were to predict the individual concentrations at 12 hour post-dose for patients in P1066 Cohorts IV (1 of 8 patients) and V (8 of 11 patients) who did not have an observed 12 hour C_{trough} sample collected during the intensive PK collection period; Secondary objectives included estimation of patients demographics and other covariates influencing the PK of raltegravir after oral administration in a pediatric population

Clinical Data: The analysis includes data from the adult formulation study (P068) and the pediatric PK and efficacy study (P1066), where the EC and GFS formulations were dosed. Data from P1066 Cohourts I and IIA from children administered poloxamer film coated tablets (adult tablets) have been described in prior reports and were not included in this analysis. P068 treatment A (administered poloxamer tablet) and treatment D (EC administered with high fat meal) data were also not included. Blood samples in study P068 were collected from predose to up to 72 hour post-dose (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, and 72 hour). PK samples collected in study P1066 included intensive samples at predose , 0.5, 1, 2, 3, 4, 6, 8, and 12 hour post-dose for Cohort IIB and III; Cohort IV (predose, 0.5, 1, 2, 4, and 12 hour) and cohort V (predose, 0.5, 1, between 3-5, and between 8-10 hour). Sparse samples collected in study 1066 included those at weeks 4, 8, 12, and 24).

Methods: A two-compartment model similar to previously developed model was used to characterize the data (Figure 6). NONMEM version VII (Globomax, Hanover, MD) was used in the analysis. Model fitting was performed in a UNIX environment with Intel FORTRAN Compiler. Xpose, PsN and R were used for the exploratory analysis and post NONMEM analysis.

Figure 6: Diagram of two compartment population PK model structure



Continuous covariates including weight, age and body surface area were included in the model using power equation after centering on the median as shown in the following equation

$$P^* = \theta_x \cdot \left(\frac{Covariate}{Covariate\ \text{Median}} \right)^{\theta_y}$$

Where P* is a typical value of a pharmacokinetic parameter P, and θx and θy are fixed-effect parameters to be estimated. Categorical covariates including race, sex, and food intake were incorporated into the model as categorical covariates as follows: $P^* = \theta x \cdot \theta z^{Q}$

where Q is an index variable that has a value of 1 in the presence of the covariate, otherwise it has a value of 0.

Results:

The population PK parameter estimates for the final model (run 302) are summarized in Table 13.

Table 13: Summary of raltegravir PK final model parameter estimates and bootstrap confidence interval for model parameters

Parameters	Population estimates (%RSE)	Bootstrap median [90% CI][a] of population estimates	IIV[b] (%RSE)	Bootstrap median [90%CI] of IIV
V2 (L)	3.51 (22.4)	3.54 [2.31, 4.67]	107.7 (29.1)	106.3 [79.7, 138.9]
V3 (L)	27 (11.8)	27.1 [22.5, 31.3]	---	---
CL (L/hr)	9.72 (5.5)	9.69 [8.96,10.7]	33.9 (26.4)	33.3 [26.3, 40.7]
Q (L/hr)	0.865 (12.6)	0.861 [0.68, 1.07]	55.9 (35.6)	54.8 [35.4, 69.2]
KA (intensive PK) (1/hr)	0.723 (5.4)	0.726 [0.663, 0.801]	31.8 (34.2)	30.8 [17.2, 40.1]
KA (sparse PK) (1/hr)	0.723 (5.4)	0.726 [0.663, 0.801]	94.5 (36.3)	94.3 [66, 122]
F1 (bioavailability)	1 (---)	1 [1, 1]	46.0 (26.9)	44.9 [34.9, 54.4]
Proportional error (intensive PK)	0.15 (15.1)	0.15 [0.12, 018]	---	---
Proportional error (sparse PK)	0.47 (13.5)	0.47 [0.38, 0.59]	---	---
Additive error	4.9 (18.4)	4.77 [3.61, 6.54]	---	---

[a] Median value and 90% confidence interval were calculated using 500 re-sampled and 74% converged bootstrapping runs. The lower and upper limits for 90% CI were calculated as 5th and 95th percentiles, respectively.

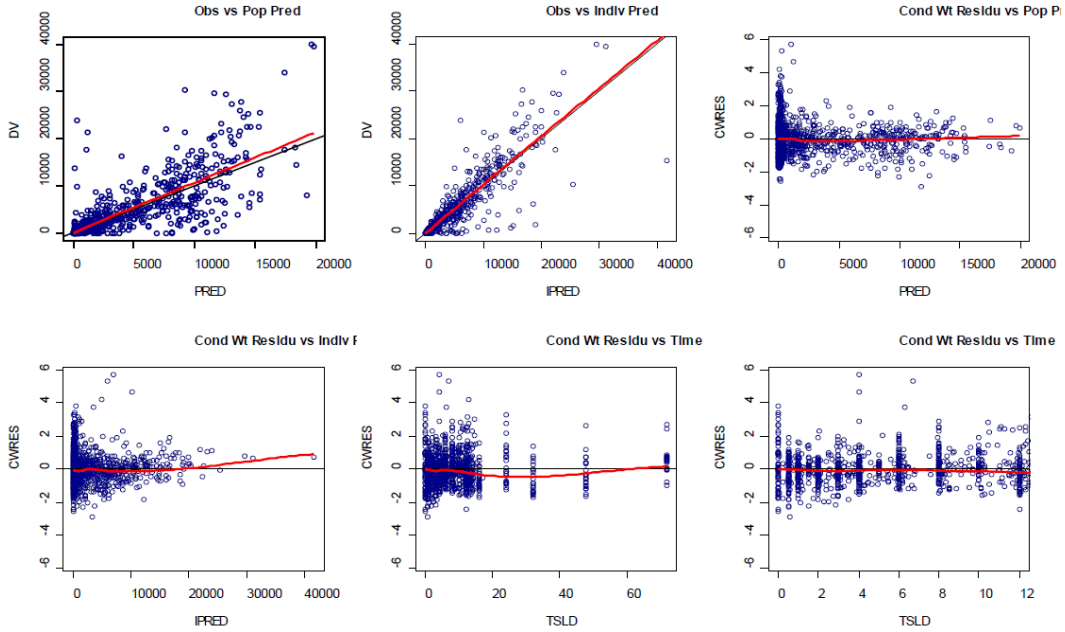
[b] IIV: Interindividual variability, calculated as $(variance)^{1/2}*100(\%)$.

Source: *Source: Table 11 on Page 27 of the* (b) (4) *analysis report*

Basic Goodness-of-fit plots for the final model

The basic goodness-of-fit plots for the final model are presented in Figure 7 as follows

Figure 7: Basic goodness-of-fig plots for the final model

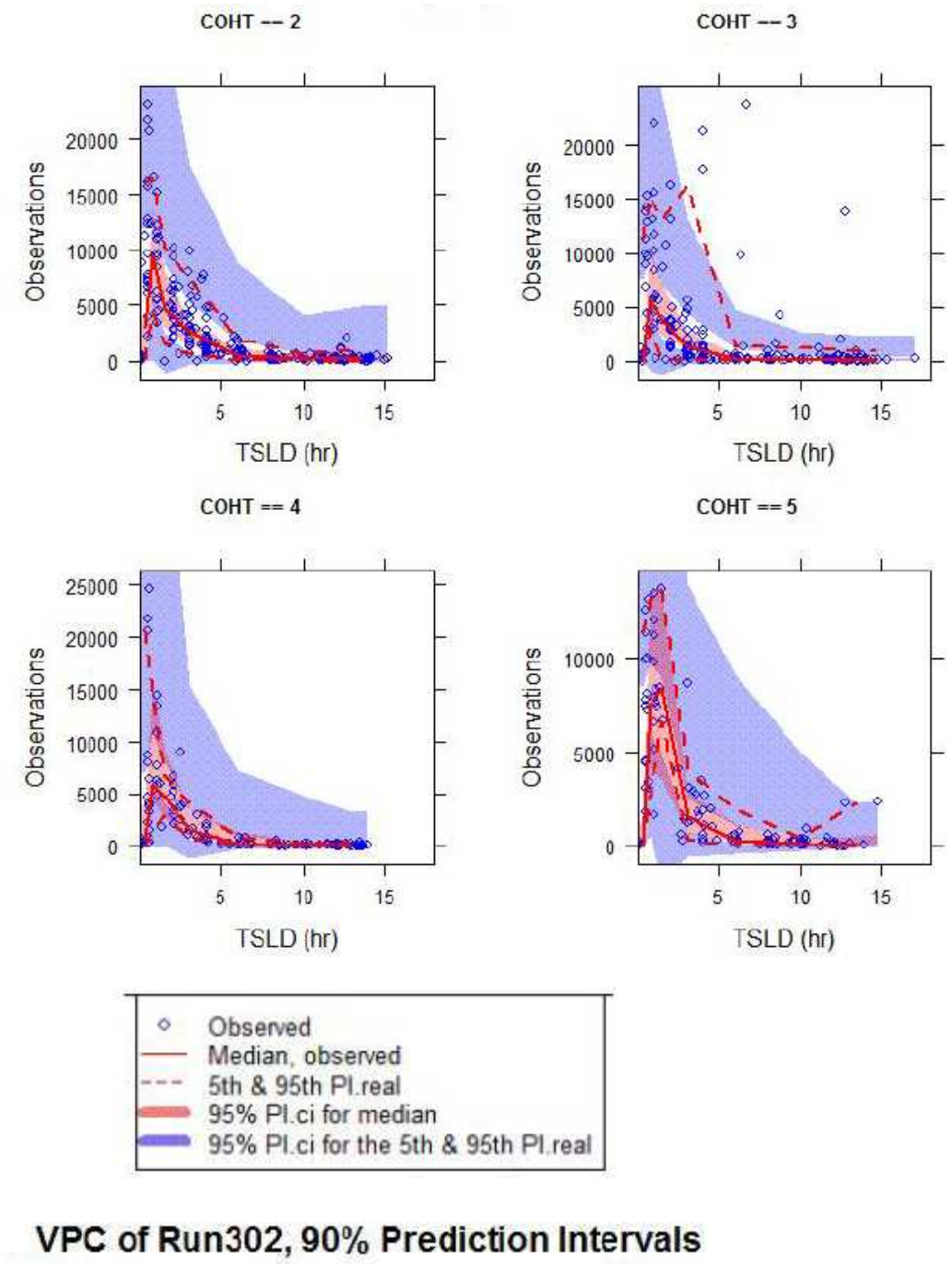


Source: Figure 7 on Page 29 of the (b) (4) *analysis report*

Model Qualification

The final model was evaluated using a visual predictive check (VPC) for concentration versus time grouped by study and cohort. The VPC plots are displayed in Figure 8.

Figure 8: Visual Predictive Check (VPC) plot of final model



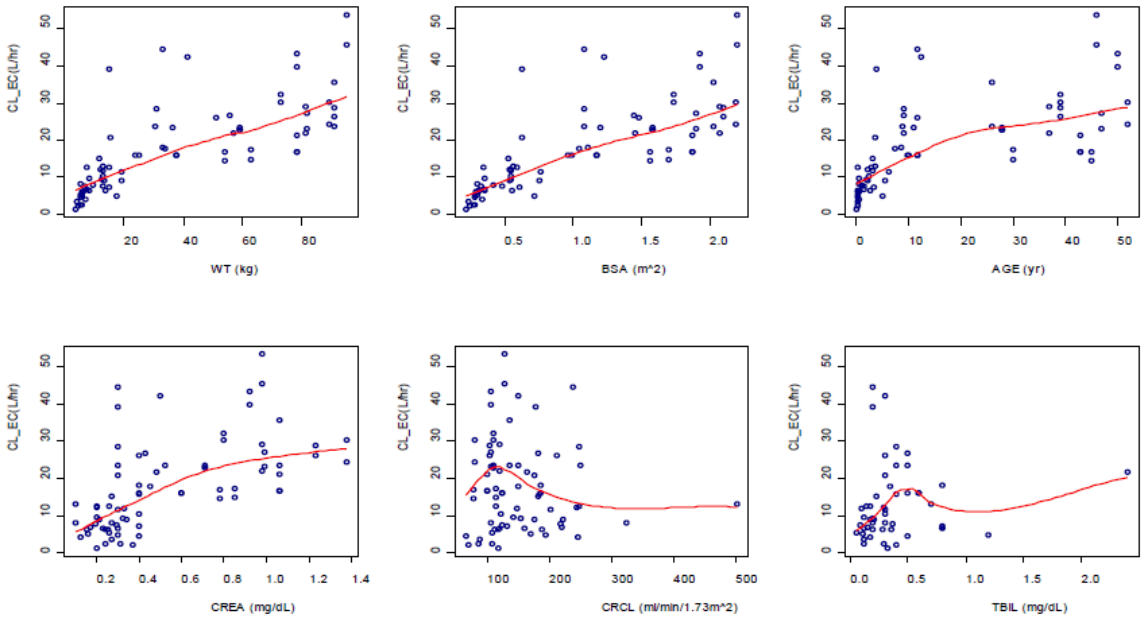
Source: Figure 10 on Page 33 of the (b) (4) *analysis report*

Covariates on Raltegravir PK

The sponsor explored relationship between raltegravir clearance and various covariates. Body weight was identified as a significant covariate. Other covariates such as BSA and Age was also found significant but they are highly correlated to body weight, therefore, only body weight was included in the final model

Relationship between raltegravir exposure and body weight was plotted in Figure 9

Figure 9: Oral clearance (CL/F) versus Covariates



Source: Figure 4 on Page 23 of the (b) (4) *analysis report*

Reviewer's Comment:

The sponsor's final mode is acceptable from the goodness-of-fit plots and VPC analysis. The model seems adequate in describing the observed data. The estimates of PK parameters appear reasonable. The sponsor only included raltegravir PK data from P068 and P1066 where patients or healthy volunteers were administered granules for suspension or chewable tablets. This approach was reasonable as the results from P068 demonstrated that the adult poloxamer tablets had different absorption and bioavailability compared to the two pediatric formulations and as the PK data from Cohort I and IIA, which used the adult poloxamer formulation, was previously reviewed. In the current analysis, the sponsor did not include a parameter for formulation effects on absorption or bioavailability. Instead, the sponsor coded a 33% formulation difference into the population PK model to account for lower bioavailability from the chewable tablet formulation compared to the GFS. The reviewer acknowledges this approach was used due to limited total available data and while not ideal, was acceptable given the available information and did not impact identification of a population PK model that describes raltegravir PK in pediatrics.

The sponsor did not explore the relationship between body weight and raltegravir exposure. With submitted data including patients from all five cohorts, the reviewer

plotted exposure (AUC_{12}, C_{max}, and C_{12hr}) versus body weight after administration of the proposed dosing regimen. AUC_{12} and C_{12hr} were found comparable across all cohorts and body weight range, but C_{max} in children less than 20 kg was higher than those heavier than 20 kg. There was insufficient information in Cohorts IV and V to determine whether the increased C_{max} may be a safety concern, though no relationship between raltegravir exposure and key safety events had been identified in previous reviews.

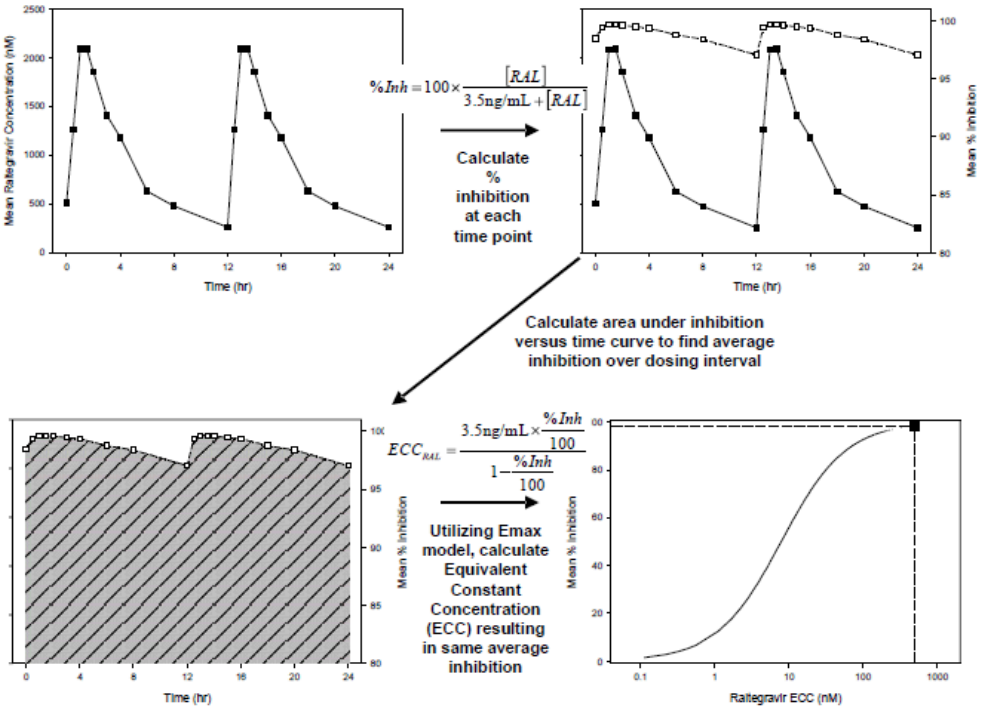
PK/PD Viral Dynamics Model Analyses

The sponsor constructed a PK/PD viral dynamics model to evaluate the exposure-response relationship of raltegravir and viral inhibiting. The model quantifies the relationship between the Equivalent Constant Concentration (ECC) and percent of viral inhibition. The following schematic (Figure 10) describes how the ECC value was calculated. The sponsor used this approach to calculate an ECC value for the observed raltegravir PK profiles for Cohorts I and V and compared these results to the calculated ECC values for adults administered 400 mg BID or800 mg QD treatment from Protocol 071 (QDMRK) trial. Table 14 summarizes geometric mean (GM) ECC by pediatric cohort. For comparisons, raltegravir 800 mg QD, which did not demonstrate non-inferiority to raltegravir 400 mg BID, has a predicted GM ECC value of 49 ng/mL and the lowest percent viral inhibition of 93.3% of all the regimens. In contrast, GM ECC values of the pediatric cohorts are all exceeded the ECC predicted for 800 mg QD.

The ER curve (Figure 3) of viral inhibition and ECC showed that the calculated ECC of children 4 weeks to < 2 years old (Cohorts IV and V) lied on top of the curve and was similar to that of adults administered 400 mg BID and pediatric patients from the other cohorts (I to III).

In addition, Table 15 summarized the percentage of patients with C_{trough} < 45 nM (sponsor determined threshold for efficacy) by pediatric cohorts as well as adult patients administered 800 mg QD or 400 mg BID in study QDMRK. Patients in Cohorts IV and V showed a similar percentage of patients with C_{trough} < 45 nM to that observed in adults administered 400 mg BID providing additional evidence that the exposure in pediatrics 4 weeks to < 2 years of age may be adequate.

Figure 10: Schematic of Conversion of the Raltegravir PK Profile into an ECC Value Utilizing a Sigmoidal E_{max} Model for Viral Inhibition (400 mg BID Data used as Example)



Source: Figure 9-3 on page 90 of sponsor's report P022v1

Table 14: Calculated Geometric Mean Steady State ECC Values and Corresponding %CV for Each Cohort (I-V) of IMPAACT Protocol 1066 and Both Treatment Arms of Protocol 071 (QDMRK)

Study	Cohort: (Formulation, Age) / Study Arm	N	Dose	ECC Geometric Mean and %CV (ng/mL)	Percent Inhibition at GM ECC (%CV)
IMPAACT Protocol 1066	Cohort I: Adult tablet, 12-18 years	8	400 mg BID	235 (93.9%)	98.5% (2.3%)
	Cohort IIA: Adult tablet, 6-11 years	8	400 mg BID	134 (120.5%)	97.5% (5.6%)
	Cohort IIB: Chewable tablet, 6-11 years	10	Approx. 6 mg/kg BID	156 (58.9%)	97.8% (1.1%)
	Cohort III: Chewable tablet, 2-5 years	12	Approx. 6 mg/kg BID	92 (47.5%)	96.3% (2.7%)
	Cohort IV: GFS, 6 months - <2 years	8	Approx. 6 mg/kg BID, according to proposed dosing table	115 (47.5%)	97.1% (1.5%)
	Cohort V: GFS, 4 weeks - <6 months	11	Approx. 6 mg/kg BID, according to proposed dosing table	119 (80.2%)	97.1% (2.9%)
Merck Protocol 071 (QDMRK)	400 mg BID	20	400 mg BID	217 (108.3%	98.4% (2.5%)
	800 mg QD	22	800 mg QD	49 (90.2%)	93.3% (7.6%)

Data Source: [16.4.4; 16.1.12.16]

Source: Table 11-17 on Page 166 of Sponsor's report P022v1

Table 15: Geometric Mean C_{trough} Values and Corresponding Proportion of Patients below 45 nM C_{trough} for Each Cohort (I-V) of IMPAACT Protocol 1066 and Both Treatment Arms of Protocol 071(QDMRK)

Study	Cohort: (Formulation, Age) / Study Arm	Dose	Geometric Mean C_{trough} in nM (%CV)	N	n < 45 nM	% of patients < 45 nM
IMPAACT Protocol 1066	Cohort I: Adult tablet, 12-18 years	400 mg BID	332.63 (78)	8	0	0%
	Cohort IIA: Adult tablet, 6-11 years	400 mg BID	246.09 (221)	8	1	13%
	Cohort IIB: Chewable tablet, 6-11 years	Approx. 6 mg/kg BID	129.60 (88)	10	0	0%
	Cohort III: Chewable tablet, 2-5 years	Approx. 6 mg/kg BID	71.16 (55)	12	2	17%
	Cohort IV: GFS, 6 months - <2 years	Approx. 6 mg/kg BID, according to proposed dosing table	108.2 (52)	8	0	0%
	Cohort V: GFS, 4 weeks - <6 months	Approx. 6 mg/kg BID, according to proposed dosing table	116.6 (68)	11	1	9%
Merck Protocol 071 (QDMRK)	400 mg BID	400 mg BID	257 (167)	20	1	5%
	800 mg QD	800 mg QD	40 (111)	22	12	55%

Data Source: [16.1.12.10; 16.1.11.14; 16.1.12.14]

Source: Table 11-14 on Page 162 of Sponsor's report P022v1

Reviewer's Comment: Based on sponsor's analysis, there existed a clear relationship between ECC and percentage of virus inhibition; however, we do not have a direct relationship between ECC and virologic success rate. It was previously observed that 800 mg QD failed to achieve non-inferiority in a comparative trial with 400 mg BID, so it can be assumed that exposures approaching C_{tr} and ECC values for this regimen may likewise be considered as suboptimal. The assessments performed by the sponsor demonstrate that the C_{tr} and ECC for the proposed pediatric regimens exceed that for the 800 mg QD in adults and are similar to those for 400 mg BID in adults.

In addition, from the ER curve, we found that the ECC value achieved by patients 2 to 6 years age (Cohort III) administered chewable tablets was even lower than ECC in adult patients administered raltegravir oral tablets 100 mg BID. The GM C_{12hr} of patients in Cohort III (71 nM) is only about half of that in adult patients administered 400 mg BID (142 nM). The apparently lower exposure in Cohort III may suggest an optimal dose for this pediatric age group administered the chewable tablet formulation has not reached and a higher dose may be needed.

4 Reviewer's Analysis

4.1 Introduction

The reviewer performed independent analyses to compare raltegravir exposure and efficacy in patients 4 weeks to less than 2 years (Cohorts IV and V) to that in pediatric patients from Cohort I through III and to adults.

4.2 Objectives

The objectives of the reviewer's analysis were as follows:

1) To simplify the proposed pediatric dosing table while maintaining similar exposures within pediatric dosing categories
2) To compare the PK parameters and antiretroviral efficacy of raltegravir in Cohort I to V to assess the adequacy of exposure and similarity of efficacy in patients 4 weeks to less than 2 years of age administrating the proposed dosing regimen.
3) To evaluate the viral time course in pediatrics from Cohorts IV and V based on baseline, week 24, week 48, and virologic failure assessments

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 16.

Table 16: Analysis Data Sets

Study Number	Name	Link to EDR
P022	pkderiv2.xpt	\\Cdsesub1\evsprod\NDA205786\0000\m5\datasets\p022v1\p022\listings\hpbio
P022	pkpd.xpt	\\Cdsesub1\evsprod\NDA205786\0000\m5\datasets\p022v1\p022\listings\hpbio
P022	nonmem.xpt	\\Cdsesub1\evsprod\NDA205786\0000\m5\datasets\p022v1\p022\listings\hpbio
P022	hivrsst.xpt	\\Cdsesub1\evsprod\NDA205786\0000\m5\datasets\p022v1\p022\listings\microbiology

4.3.2 Software

SAS for Windows 9.3 was used for all statistical analysis and graphing. NONEM 7.2 on a sun grid engine cluster of six Redhat enterprise servers was used for population PK analyses.

4.4 Results

4.4.1 Pediatric Dosing Recommendations

The sponsor's proposed dosing table (Table 1) for children 4 weeks (b) (4) (b) (4) included eight dosing groups, based on a dose at 6 mg/kg. The weight range within some of these groups was as narrow as <1 kg. Given the relative rapid change in body weight for pediatrics in this age range, the reviewer recommended a simplified table as demonstrated in Table 2. The new table maintained a pediatric dosing target of 6 mg/kg

but allowed individual dosing range to vary between 80-125% of the 6 mg/kg target compared to between (b) (4) of the 6 mg/kg target as was proposed in the sponsor's table.

As shown in Table 17, the reviewer's proposed dosing table will not impact dosing in a majority of pediatrics 4 weeks (b) (4). In addition, the simplified dosing regimen reduces the originally proposed (b) (4) dosing categories to six dosing categories. Only pediatric patients with body weights between 3.7-4.5 kg, 7.6-9.0 kg, and 11-11.4 kg will have altered dosing with the FDA's proposed dosing compared to that proposed by the sponsor. Of these pediatrics, only patients with body weight 3.7-3.9 kg and 7.6-7.9 kg will have receive a reduced dose compared to that proposed by the sponsor. These proposed dosing changes are illustrated graphically in Figure 11 and show that a majority of pediatric patients in study P022 will have received identical doses with the proposed regimen as were administered in the study. Overall, with the updated proposed pediatric dose patients 4 weeks (b) (4) will receive a dose between 4.8 mg/kg to 7.5 mg/kg.

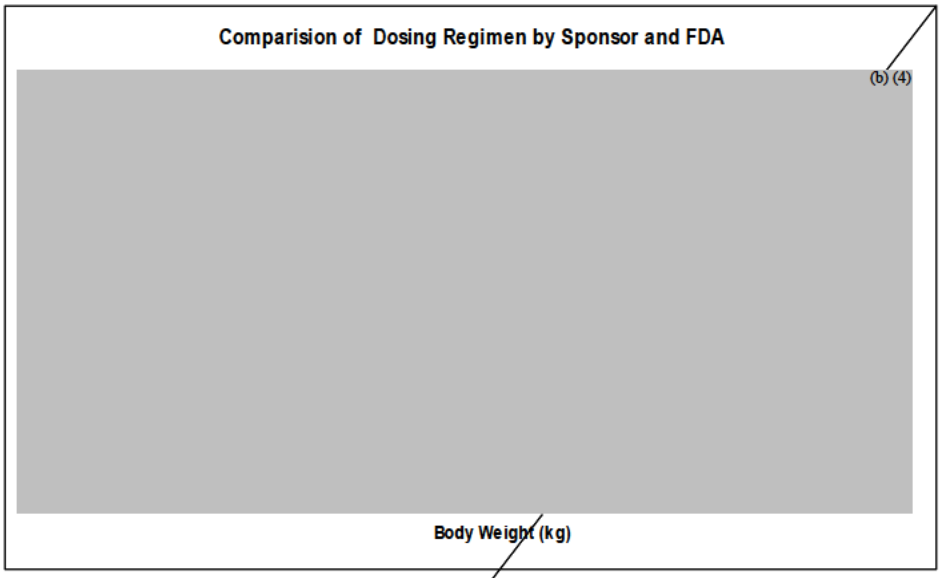
Table 17: Summary of Individual Ratio of Given Dose versus Calculated Dose by the Sponsor and FDA in Patients 4 Weeks (b) (4)

Body Weight (kg)	Calculated Dose (6 mg/kg)	Sponsor Dose (kg)	Ratio of Sponsor Dose/Calculated Dose	FDA Dose (mg)	Ratio of FDA dose /Calculated Dose	Diff of FDA and Sponsor Dose
3	18	20	1.11	20	1.11	0
3.1	18.6	20	1.08	20	1.08	0
3.2	19.2	20	1.04	20	1.04	0
3.3	19.8	20	1.01	20	1.01	0
3.4	20.4	20	0.98	20	0.98	0
3.5	21	20	0.95	20	0.95	0
3.6	21.6	20	0.93	20	0.93	0
3.7	22.2	(b) (4)		20	0.90	(b) (4)
3.8	22.8			20	0.88	
3.9	23.4			20	0.85	
4	24			30	1.25	
4.1	24.6			30	1.22	
4.2	25.2			30	1.19	
4.3	25.8			30	1.16	
4.4	26.4			30	1.14	
4.5	27			30	1.11	
4.6	27.6	30	1.09	30	1.09	0
4.7	28.2	30	1.06	30	1.06	0
4.8	28.8	30	1.04	30	1.04	0
4.9	29.4	30	1.02	30	1.02	0
5	30	30	1.00	30	1.00	0
5.1	30.6	30	0.98	30	0.98	0
5.2	31.2	30	0.96	30	0.96	0
5.3	31.8	30	0.94	30	0.94	0
5.4	32.4	30	0.93	30	0.93	0
5.5	33	30	0.91	30	0.91	0

5.6	33.6	30	0.89	30	0.89	0
5.7	34.2	30	0.88	30	0.88	0
5.8	34.8	30	0.86	30	0.86	0
5.9	35.4	30	0.85	30	0.85	0
6	36	40	1.11	40	1.11	0
6.2	37.2	40	1.08	40	1.08	0
6.4	38.4	40	1.04	40	1.04	0
6.6	39.6	40	1.01	40	1.01	0
6.8	40.8	40	0.98	40	0.98	0
7	42	40	0.95	40	0.95	0
7.2	43.2	40	0.93	40	0.93	0
7.4	44.4	40	0.90	40	0.90	0
7.6	45.6	(b) (4)		40	0.88	(b) (4)
7.8	46.8			40	0.85	
7.9	47.4			40	0.84	
8	48			60	1.25	
8.2	49.2			60	1.22	
8.4	50.4			60	1.19	
8.6	51.6			60	1.16	
8.8	52.8			60	1.14	
9	54			60	1.11	
9.2	55.2	60	1.09	60	1.09	0
9.4	56.4	60	1.06	60	1.06	0
9.6	57.6	60	1.04	60	1.04	0
9.8	58.8	60	1.02	60	1.02	0
10	60	60	1.00	60	1.00	0
10.2	61.2	60	0.98	60	0.98	0
10.4	62.4	60	0.96	60	0.96	0
10.6	63.6	60	0.94	60	0.94	0
10.8	64.8	60	0.93	60	0.93	0
10.9	65.4	60	0.92	60	0.92	0
11	66	(b) (4)		80	1.21	(b) (4)
11.2	67.2			80	1.19	
11.4	68.4			80	1.17	
11.6	69.6	80	1.15	80	1.15	0
11.8	70.8	80	1.13	80	1.13	0
11.9	71.4	80	1.12	80	1.12	0
12	72	80	1.11	80	1.11	0
12.2	73.2	80	1.09	80	1.09	0
12.4	74.4	80	1.08	80	1.08	0
12.6	75.6	80	1.06	80	1.06	0
12.8	76.8	80	1.04	80	1.04	0
13	78	80	1.03	80	1.03	0
13.2	79.2	80	1.01	80	1.01	0
13.4	80.4	80	1.00	80	1.00	0
13.6	81.6	80	0.98	80	0.98	0
13.8	82.8	80	0.97	80	0.97	0
13.9	83.4	80	0.96	80	0.96	0

14	84	100	1.19	100	1.19	0
15	90	100	1.11	100	1.11	0
16	96	100	1.04	100	1.04	0
17	102	100	0.98	100	0.98	0
18	108	100	0.93	100	0.93	0
19	114	100	0.88	100	0.88	0
20	120	100	0.83	100	0.83	0

Figure 11: Dose/Weight versus Body Weight by Sponsor-Proposed and FDA Recommended Dosing Regimen



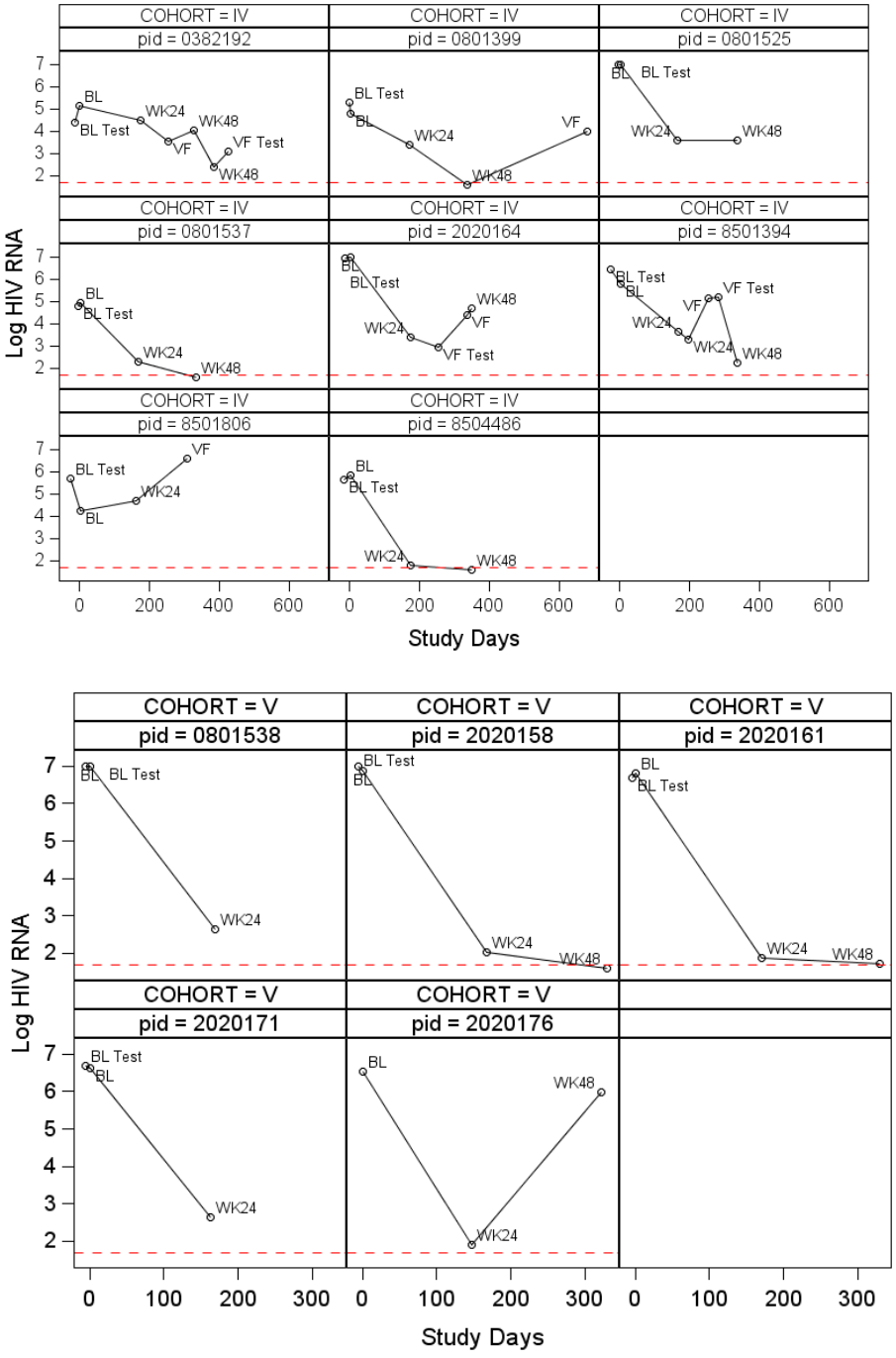
4.4.2 Summary of Raltegravir PK and Efficacy in Pediatrics 4 weeks to Less Than 2 Years of Age

Raltegravir efficacy and PK data for pediatric patients in Cohorts IV and V compared to other pediatric cohorts and adults are summarized in the QBR questions (Section 2.3).

4.4.3 Virus profile of Children 4 weeks to less than 2 years of age who failed to meet HIV RNA < 50 copies/mL at Week 24

The change in virus profile in children 4 weeks to less than 2 years of age who failed to meet HIV RNA < 50 copies/mL at Week 24 was plotted in Figure 12. This data demonstrates that the time of assessment (24 weeks) may not have been sufficient for all pediatrics to achieve < 50 HIV RNA copies/mL. This is evident as some children who failed to reach the target of less than HIV RNA 50 copies at week 24 continued to have declining viral levels and achieved the targeted viral suppression by week 48.

Figure 12: Virus Profile of Patients 4 Weeks to < 2 Years Old with HIV RNA >50 copies/mL at Week 24



5. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Pkpd.sas	Pk and Pd analysis	\\cdsnas\pharmacometrics\\Raltegravir_NDA205786_FI\ER Analyses\Reviewer\

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FANG LI
11/06/2013

JEFFRY FLORIAN
11/06/2013

ISLAM R YOUNIS
11/06/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205786 22145 S-031 203045 S-009	**Brand Name**	Isentress
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	Raltegravir
Medical Division	**DAVP**	**Drug Class**	**HIV Integrase Inhibitor**
OCP Reviewer	**Fang Li**	**Indication(s)**	**HIV-1 Infection**
OCP Team Leader	**Islam Younis**	**Dosage Form**	(b) (4) **Suspension**
Pharmacometrics Reviewer	**Fang Li/Jeffry Florian**	**Dosing Regimen**	**Weight based, twice daily**
Date of Submission	**June 26, 2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**Nov 18, 2013**	**Sponsor**	**Merck**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**Dec 26, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:	**X**	**1**	**1**	**P022V1 (4 weeks to <2 years)**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**1**		**Report and data only, appendix 2 missing**
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**x**			
Total Number of Studies		**3**	**1**	**Population PK report to be reviewed**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Not CDISC format, not required for this application
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	x			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Fang Li, Ph.D.	8/1/2013
Reviewing Clinical Pharmacologist	Date
Islam R. Younis, Ph.D.	8/1/2013
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FANG LI
08/06/2013

JEFFRY FLORIAN
08/06/2013

ISLAM R YOUNIS
08/06/2013