CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203045Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS PRODUCT QUALITY REVIEW

NDA Number	203-045 (original NDA)
Product name, generic name of the active, and strength and dosage form	**Isentress® (raltegravir potassium), 25-mg and 100-mg Chewable Tablets**
Submission date	6/30/2011
Applicant	Merck Sharp and Dohme Corp., Rahway, New Jersey
Medical Division	Anti-viral Drug Products
Type of Submission	Quality, 505 b(1)
Primary CMC/Quality Reviewer	Andrew Yu, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

SUBMISSION

This submission/application includes safety, efficacy, pharmacokinetic and product quality data.

The studies in this submission are for supporting weight-based dosing of raltegravir chewable tablets, targeting approximately 6-8 mg/kg raltegravir BID, to a maximum of 300 mg BID for pediatric patients 2 years to 12 years old.

The chewable tablet, submitted in this NDA, was studied in pediatric patients (2 years to 12 years old) who may not be able to swallow tablets or who may need different dosage strength. Although the 50-mg raltegravir chewable tablet was also studied in IMPAACT P1066, currently, only the 25-mg and 100-mg tablet strengths are proposed for marketing. The 100-mg tablets are scored to provide the 50-mg strength.

In addition, this submission provides a single dose comparative pharmacokinetic study of raltegravir formulations, evaluated in healthy 12 adult subjects. The results of this study entitled, **"Relative Bioavailability of a Raltegravir Pediatric Ethycellulose Chewable Tablet Formulation, a Raltegravir Oral Granules For Suspension Formulation, and the Raltegravir Adult Formulation In Healthy Adults (Protocol 068)"**, showed that the raltegravir proposed-to-be marketed chewable tablets at 400-mg dose (four 100-mg tablets) and the currently marketed 400-mg raltegravir tablets are bio-inequivalent. As evident from the differences in the formulations, the in vitro and the in vivo performance of the raltegravir proposed-to-be marketed chewable tablets and the currently marketed raltegravir tablets are significantly different and they are not interchangeable.

EXECUTIVE SUMMARY AND RECOMMENDATIONS

- The raltegravir chewable tablets are taste-masked and its chewability, as assessed by its mean crush strength and tablet hardness, is suitable for the target patient population.

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- Tablet hardness is based on breakability characteristics as well as the intended chewability characteristics for the 2 to 12 year old children. Tablet hardness boundaries are within those required for acceptable chewability of the tablets.
- The selected dissolution method is robust and consistent with the intended in vitro and in vivo performance of the product. The proposed dissolution acceptance criterion (Q (b) (4) at 15 min) is meaningful based on the submitted data and is acceptable.
- Rapid dissolution in the selected medium is consistent with a typical tmax of 1 hr or less.
- The observed high variability in absorption of raltegravir may be explained by permeability differences as well as its solubility characteristics (References 1 and 2). Furthermore, the impact of differences in drug release from the adult raltegravir tablets and the chewable tablets is also evident in the summary data included in the Appendices 1 and 2 (pages 30-40 of this review).

  It is noted that the raltegravir chewable tablets are characterized as a Biopharmaceutics Classification System (BCS) 2 drug product (poorly soluble and highly permeable) whereas the adult raltegravir tablet was characterized as a BCS 4 (poorly soluble and poorly permeable) drug product. For purposes of this review, given the differences in the methodology for assessing bioavailability and the intended differences in the release patterns, the differences in the BCS classification of the tablets is not as critical; however, given the continuation of development of pediatric dosage forms for raltegravir, this reviewer believes that understanding of the in vivo drug release from these formulations and the factors influencing their release is important particularly, for pediatric patients. Due to growth and maturational changes as well as differences in dietary needs, in vivo performance of drug products may be significantly different in pediatric patients. This point may be of particular focus for the pediatric patients less than 2 years old as this group is the most "vulnerable" age group compared to the older pediatric patients. (b) (4)

Comment that may be communicated to the Applicant:

(b) (4)

(b) (4)

Reference ID: 3054899

Recommendations

Recommendation and Conclusion on Approvability

Following review of the biopharmaceutics information in this NDA 203-045 related to the pediatric raltegravir chewable tablets, the submitted information is adequate, the following proposed dissolution method and the dissolution acceptance criterion are acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance criterion
No. 2 (paddle)	50 rpm	900mL	37°C	Deaerated Water	Q = (b) (4) at 15 min

From a Biopharmaceutics perspective, NDA 203-045 for Isentress® (raltegravir potassium), 25-mg and 100-mg Chewable Tablets is recommended for approval.

SIGNATURES

Arzu Selen, Ph.D.
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Office of New Drug Quality Assessment

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NDA 203-045 RALTEGRAVIR CHEWABLE TABLETS - BIOPHARMACEUTICS EVALUATION

I. BACKGROUND

Raltegravir is a human immunodeficiency virus integrase strand transfer inhibitor and is formulated as raltegravir potassium oral tablets (Isentress®).

The 400-mg Isentress film-coated tablets (also referred to as adult tablets or non-chewable tablets) were approved in 2007 under NDA 022-145, and are indicated for use in combination with other anti-retroviral agents for the treatment of HV-1 infection in adult patients. In 2009, the indication was broadened to include treatment-naïve HIV infected patients. The typical adult dose for these tablets is 400-mg twice daily without regard to meals.

To support the age-appropriate use of the 400-mg ISENTRESS® tablets in pediatric patients, the Applicant submitted simultaneously with this NDA for the chewable tablets, a supplement to NDA 022-145 (S-022) for providing clinical, statistical and labeling data for the 400-mg tablets. The Applicant has identified this chewable tablet NDA (NDA 203-045) and the efficacy supplement (NDA 022-145, S-022) as the raltegravir pediatric submission for pediatric patients 2 through 18 years of age. The following table, Table 1, lists the studies provided in NDA 022-145 S-022 (DARRTS SDN-0199).

Table 1

Overview of Data Provided in the Raltegravir Pediatric Application (2 through 18 years)

TABLET TYPE	PATIENT AGE
Complete PK and 24-Week, Safety and Efficacy Data	
Adult (400 mg) tablet	12 through 18 years
Adult (400 mg) tablet	6 through 11 years and weighing ≥25kg
Chewable tablet	6 through 11 years
Chewable tablet	2 through 5 years
Complete 48-Week Safety and Efficacy Data	
Adult (400 mg) tablet	12 through 18 years
Adult (400 mg) tablet	6 through 11 years and weighing ≥25kg
Chewable tablet	6 through 11 years
Long-Term Complete Week-80 Safety and Efficacy Data	
Adult (400mg) tablet	12 through 18 years

For pediatric development, several formulations of raltegravir were studied and are listed in Table 2.

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Table 2

Raltegravir Formulations Used in Studies to Support Pediatric Development

Protocol	Protocol Description	Dosage	Batch Number	Formulation Category
020	An Open-Label, 4-Period, Crossover Study to Investigate the Pharmacokinetics of a Single Oral Dose of the MK-0518 Pediatric and Adult Tablet Formulations in Healthy Adults	100 mg	WL00006542‡	Adult clinical Tablet
		100 mg	WL00014063	Pediatric (b) (4) (b) (4) Tablet (b) (4)
		400 mg	WL00010064‡	Adult Clinical Tablet
		400 mg	WL00014819	(b) (4) Tablet
031	An Open-Label, 2-Period, Crossover Study to Investigate the Pharmacokinetics of a Single Oral Dose of the MK-0518 Pediatric Ethylcellulose and Adult Poloxamer Tablet Formulations in Healthy Adults	100 mg	WL00022782	Pediatric (b) (4) (b) (4) Tablet (b) (4) Ethylcellulose
		100 mg	WL00006542‡	Adult Clinical Tablet
068	A Single-Dose Study to Compare the Pharmacokinetics of 3 Formulations of MK-0518/Raltegravir and Evaluate the Effect of Food on the Pharmacokinetics of 1 Formulation	100 mg	WL00025332	Pediatric Chewable Tablet (CT) Ethylcellulose
		400 mg†	FL00005829	Pediatric Oral Granules (OG)*
		400 mg	WL00022441§	Adult Tablet
P1066 (022)	Multicenter, Open-Label, PK, Safety and Efficacy Study in Pediatric Patients ≥4 Weeks to 18 Years of Age	100 mg	WL00024847§	Adult Tablet
		200 mg	WL00016983§ WL00016984§	Adult Tablet
		400 mg	WL00022057§ WL00027022§ WL00028667§ WL00029889§ WL00036686§ WL00037857§	Adult Tablet
		25 mg	WL00025330 WL00035279 WL00036782	Pediatric Chewable Tablet (CT) Ethylcellulose
		50 mg	WL00025333 WL00032660 WL00036205 WL00036783	Pediatric Chewable Tablet (CT) Ethylcellulose
		100 mg	WL00025332 WL00032667 WL00036204 WL00036784	Pediatric Chewable Tablet (CT) Ethylcellulose
		100 mg per sachet	WL00034285 WL00038299	Pediatric Oral Granules (OG)*
* (b) (4) † ‡ §				

As listed above, the adult tablet formulation (erodible tablet formulation, 100 mg, 200 mg, and 400 mg strengths), the pediatric chewable tablet formulation (25 mg, 50 mg, and 100 mg strengths), and the oral granules for suspension were selected for further evaluation in the pediatric pharmacokinetic, safety and efficacy study in HIV-infected pediatric population (P1066). This study is also identified as IMPAACT P1066, "A Phase I/II, Multicenter, Open-Label, Non-comparative Study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials

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(IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents."
The three raltegravir formulations: a tablet (non-chewable, erodible, the approved 400-mg tablet also referred to as poloxamer tablet, adult tablet), a chewable tablet (under review, this NDA), and oral granules for suspension (b) (4) .

For biopharmaceutics assessment of the approved 400-mg non-chewable raltegravir tablets, also called adult tablets, please see Dr. Derek Zhang's Clinical Pharmacology and Biopharmaceutics review (dated 10/1/2007) and for product quality assessment, please see Dr. George Lunn's and Dr. Ted Chang's CMC-Product Quality reviews, dated 9/26/2007 and 9/28/2007.

II. BIOPHARMACEUTICS

This biopharmaceutics review is specific for biopharmaceutics/product quality characterization of the raltegravir chewable tablets and also focuses on the evaluation of the proposed dissolution method and acceptance criterion. For assessment of chemistry, manufacturing and controls of the raltegravir chewable tablets please see Dr. Andrew Yu's CMC/product quality review.

As both the chewable tablet and the non-chewable tablet are the tablet dosage forms intended for age-appropriate use in pediatric patients, biopharmaceutics information specific to the approved 400-mg tablets is also provided as additional background in APPENDIX 1.

Raltegravir chewable tablets are likely to be swallowed as well as chewed by pediatric patients and given the product composition, API characteristics, and in vitro performance in multiple media (including its rapid disintegration), in vivo drug release following ingestion (chewed or swallowed) would be similar.

A. Drug substance

Raltegravir is a white to off-white powder, soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol.

The solubility of raltegravir increases with increasing pH such that its solubility in water is approx. 71 mg/mL. Its pKa is 6.3. The pH of a saturated solution of raltegravir in water was 9.9. Raltegravir solubility in typical physiological pH range is as follows.

Table 3: Raltegravir Solubility

Medium	Raltegravir solubility (mg/mL)
USP HCl acid buffer pH 1.2	0.014
USP Acetate buffer pH 4.5	0.020
25 mM Na phosphate buffer at pH 6.8	0.1
Water	70.79

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At pH values greater than its pKa, its solubility increases, and as dissolution continues, the pH increases and facilitates further dissolution. The pH of the un-buffered water following complete dissolution of the 400-mg raltegravir tablet was 7.9.

B. Drug Product and Product Development

Please see Dr. Yu's review for full description and assessment of the manufacturing process and controls.

(b) (4)

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/s/

ARZU SELEN
12/07/2011

ANGELICA DORANTES
12/07/2011

Office of Clinical Pharmacology Review

NDA:	203045 (raltegravir ethylcellulose chewable tablet)
sNDA:	22145 (SDN 230) (raltegravir poloxamer adult tablet)
Submission date:	June 30, 2011
Brand Name:	Isentress®
Generic Name:	Raltegravir
Primary Reviewer:	Ruben Ayala, Pharm.D.
Secondary Reviewer:	Sarah Robertson, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 4
OND Division:	DAVP
Sponsor:	Merck
Relevant IND(s):	IND69928
Submission Type; Code:	sNDA for raltegravir chewable tablets; priority review
Formulation; Strength(s):	Approved: Poloxamer adult tablets; 400 mg strength Proposed: Ethylcellulose chewable tablets; 25 mg and 100 mg scored

Proposed dosing Regimen:	Children and adolescents
	• ≥12 to ≤18 years of age:
	  ○ 400 mg BID using poloxamer adult tablets
	• ≥6 through 11 years of age (2 options)
	  ○ If ≥ 25kg: 400 mg BID using poloxamer adult tablets
	  ○ Any weight: ~6 mg/kg max (300 mg BID) using ethylcellulose chewable tablets
	• ≥2 through ≤5 years of age:
	  ○ If ≥10 kg: ~6 mg/kg (max 300 mg BID) using ethylcellulose chewable tablets

Indication:	Treatment of HIV-1 infection in combination with other antiretroviral agents in pediatric subjects ranging from 2 to 18 years of age.

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1. Executive Summary

Raltegravir, in combination with other antiretroviral agents, is currently approved for treatment-experienced and treatment-naïve adult patients infected with HIV-1. The Applicant seeks to extend raltegravir's indication to pediatric patients ranging from ≥2 years to ≤18 years of age. If approved, raltegravir will be available as the current commercial poloxamer film-coated tablets, and as newly developed ethylcellulose chewable tablets.

The Applicant conducted one Phase I/II trial with raltegravir in treatment-experienced pediatric subjects ranging from 2 through 18 years of age who failed previous therapy with at least one ARV medication (IMPAACT P1066). This clinical trial aimed to evaluate safety, efficacy, and pharmacokinetic (PK) data in pediatrics, and to determine an appropriate dose of the poloxamer tablet and ethylcellulose chewable tablet for pediatric patients. Trial results showed that raltegravir 400 mg BID and ~6 mg/kg BID, delivered as the adult or chewable tablets respectively, in combination with optimized background therapy (OBT), delivered comparable efficacy and raltegravir exposures in pediatric patients compared to adults.

In addition, Trial P068 evaluated the relative bioavailability of the 400 mg raltegravir poloxamer tablet and 100 mg ethylcellulose chewable tablet (4 X 100 mg) in healthy adults under fasted conditions, as well as the effect of a high fat meal on the bioavailability of the ethylcellulose chewable tablet.

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1.1 Recommendation

From a clinical pharmacology perspective, data submitted in the supplemental New Drug Application (sNDA) and the NDA are acceptable.

- We concur with the Applicant's proposed dosing recommendation for raltegravir in pediatric patients, but propose removing (b) (4)
  - 12 years of age and older
    - One 400 mg tablet BID.
  - 6 through 11 years of age (2 options)
    - One 400 mg tablet BID (if body weight ≥25 kg), OR
    - Weight-based dosing not to exceed (NTE) 300 mg BID using chewable tablets (see table below).
  - 2 through 5 years of age
    - Weight-based dosing NTE 300 mg BID using chewable tablets (see table below).

Table 1 Recommended dose* of Isentress chewable tablets in pediatric patients 2 through 11 years of age

Body Weight		Dose	Number of chewable tablets ~~per dose~~
(kg)	~~(lbs)~~		
(b) (4)			
10 to less than 14	~~22 to <31~~	75 mg twice daily	3 X 25 mg twice daily
14 to less than 20	~~31 to <44~~	100 mg twice daily	1 X 100 mg twice daily
20 to less than 28	~~44 to <62~~	150 mg twice daily	1.5 X 100 mg† twice daily
28 to less than 40	~~62 to <88~~	200 mg twice daily	2 X 100 mg twice daily
at least 40	~~at least 88~~	300 mg twice daily	3 X 100 mg twice daily

*The weight-based dosing recommendation for the chewable tablets is based on approximately 6 mg/kg/dose twice daily.
†The 100 mg chewable tablet can be divided into equal halves.

- We concur with the Applicant's recommendation to avoid using poloxamer tablets and ethylcellulose chewable tablets interchangeably.

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- We concur with the Applicant's recommendation that ethylcellulose chewable tablets may be administered without regard to food.

1.2 Post marketing Commitments or Requirements

There are no post marketing commitments or requirements.

1.3 Important Clinical Pharmacology and Biopharmaceutics Findings

This section describes key evidence that supports an indication for raltegravir in the treatment of HIV-1 in pediatric patients. The following two clinical trials were submitted to the Division of Antiviral Products (DAVP) for review:

1. Trial P1066 evaluated efficacy, safety, and PK of raltegravir in HIV-1 infected children.

2. Trial P068 evaluated the relative bioavailability of raltegravir when administered using poloxamer tablets and ethylcellulose chewable tablets to healthy adults, as well as the effect of a high fat meal on chewable tablets.

Trial P1066

This clinical trial was designed as a Phase I/II, randomized, open label, two stage, and multicenter trial evaluating PK, safety, tolerability, and efficacy of 48 weeks of raltegravir in HIV-infected children ≥4 weeks to 18 years of age. The current submission includes PK and efficacy results for 95 treatment-experienced children and adolescents ranging from 2 through 18 years of age receiving the final selected doses of raltegravir. Subjects were stratified by age, enrolling adolescents first, and then successively younger children. Raltegravir was administered as the adult poloxamer tablets (100, 200, and 400 mg strengths) or ethylcellulose chewable tablets (25, 50, or 100 mg strengths) as outlined below. All doses of raltegravir were administered in combination with other antiretroviral medications.

Cohort 1: Subjects ≥12 to <19 years of age received raltegravir 400 mg BID using poloxamer tablets.

Cohort 2a: Subjects ≥6 to <12 years of age received raltegravir 400 mg BID poloxamer tablets.

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Cohort 2b: Subjects ≥6 to <12 years of age received raltegravir 6 mg/kg using chewable tablets.

Cohort 3: Subjects ≥2 to <6 years of age received raltegravir 6 mg/kg using chewable tablets.

The trial was divided in two stages, 1 and 2. The trial enrolled 126 subjects overall. The initial dose-finding period enrolled 58 subjects who underwent intensive PK sampling (Stage 1). Dose selection aimed to achieve raltegravir plasma exposures ($AUC_{0\text{-}12h}$) and trough concentrations (C_{12h}) previously observed in adults.

When the adequate doses were identified, age cohorts were expanded with an additional 68 subjects to evaluate the long-term safety, tolerability, and efficacy of final recommended doses of raltegravir (Stage 2). The current database includes PK and efficacy data from 95 subjects receiving the final selected doses of raltegravir.

Identifying adequate doses of raltegravir for each age cohort (Stage 1).

Each age cohort was divided in two groups: a mini cohort (n=4) and a full cohort (n=10). Subjects in the mini-cohort received raltegravir first. If raltegravir PK and safety parameters were adequate in the mini cohort, then a full cohort was subsequently enrolled. Intensive PK was collected between 5 and 12 days following initiation of raltegravir.

The main PK targets of raltegravir in pediatrics were steady state $AUC_{0\text{-}12h}$ and C_{12h}. Pediatric doses were targeted to deliver geometric mean (GM) $AUC_{0\text{-}12h}$ values between 14 to 25 μM*hr, with individual $AUC_{0\text{-}12h}$ values ranging from 5 to 45 μM*hr. The AUC target range was based on values observed in Phase 2 trials in adults—14.3 μM*hr for raltegravir 400 mg BID monotherapy and 25.3 μM*hr for raltegravir in combination with tenofovir and lamivudine. Moreover, doses were targeted to deliver geometric mean C_{12h} values greater than 33 nM, which corresponds to the *in vitro* IC_{95} value.

As shown below, all proposed pediatric doses delivered adequate exposures of raltegravir. Subjects in Cohorts 1 and 2a received raltegravir doses ~400 mg BID using poloxamer tablets under fasting conditions. Subjects in Cohorts 2b and 3 received doses of raltegravir ~6 mg/kg BID using chewable tablets under fasting conditions. Of note, Cohorts 2a and 2b enrolled pediatric subjects in the same age and weight range but tested poloxamer and ethylcellulose tablets, respectively.

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Table 2 Summary of proposed doses and their respective steady state raltegravir exposures by cohort observed during the dose-finding period (Stage 1) in trial P1066.

Age	Cohort	Formulation	Final Recommended Dose	N†	Mean Weight	Mean Dose mg (mg/kg)	Geometric Mean (%CV) AUC_{0-12hr} (µM*hr)	Geometric Mean (%CV) C_{12hr} (nM)
12 through 18y	I	Adult tablet	400 mg BID, regardless of weight‡	11	43.55	390.91 (9.28)	15.71 (98)	332.63 (78)
6 through 11 y	IIA	Adult tablet	400 mg BID, for patients ≥25 kg	11	31.54	400.00 (13.45)	15.84 (120)	246.09 (221)
6 through 11 y	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 through 5 y	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)

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

‡ *Cohort I patients received approximately 8 mg/kg dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg the team selected 400 mg BID as the recommended dose for this age group. Patients receiving a dose other than 400 mg BID were switched; no repeat PK was performed.*

In Cohort 2a, most (7/11) subjects receiving the final recommended dose of raltegravir 400 mg BID using poloxamer tablets achieved target AUC_{0-12h} values. However, two subjects (weighing <25 kg) had 5 to 7-fold higher AUC_{0-12h} values compared to the mean cohort AUC_{0-12h} values. Investigators repeated raltegravir dosing in these two subjects at ~6 mg/kg BID using ethylcellulose chewable tablets. The new raltegravir AUC_{0-12h} values met the AUC target (see table below). Therefore, investigators recommended that the 400 mg BID dose of adult tablet only be allowed in pediatric subjects 6 through 11 years old weighing ≥25 kg. As an alternative, children in this weight group unable to swallow the tablet can also be dosed with 6 mg/kg BID of the chewable tablet.

Table 3 Comparison of raltegravir PK results in two subjects receiving raltegravir poloxamer tablets (Cohort 2a) and later switched to ethylcellulose chewable tablets (Cohort 2b) under fasting conditions.

Cohort	Subject	Formulation	Actual dose received (mg BID)	Weight (kg)	Dose (mg/kg BID)	C12h (nM)	AUC12h (uM*hr)
2a	650947F	Adult tablet	400	19.6	20.4	6815.7	88.0
2b	650947F	Chewable tablet	125	19.9	6.3	414.0	17.6
2a	730158K	Adult tablet	400	21.4	18.7	837.0	111.1
2b	730158K	Chewable tablet	150	21.1	7.1	NA	30.4

NA= Not available. No sample collected at 12 hours post dose.

Pharmacokinetic parameters of raltegravir following administration of final recommended doses during the first week of treatment (Stage 1).

Forty-four subjects underwent intensive blood sampling to define the PK of raltegravir at selected final doses. PK data were analyzed using non-

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compartmental analysis. The median T_{max} of raltegravir was faster with chewable tablets (0.5 to 1 hr) relative to poloxamer tablets (1 to 2 hr). Mean C_{max} values of raltegravir were higher (~2-fold) with the chewable tablets compared to poloxamer tablets, despite being administered at lower doses. Mean terminal half-lives of raltegravir were similar (~3 hr) using both formulations, but mean apparent oral clearance of raltegravir was lower in subjects receiving chewable tablets relative to subjects receiving poloxamer tablets. The following table summarizes the PK properties of raltegravir observed across age cohorts in Stage 1.

Table 4 PK parameters (geometric mean ± SD) of steady state raltegravir collected from all subjects participating in Stage 1 intensive PK sampling at final dose population.

Cohort	N	Dose (mg BID)	AUC_{0-12h} (μM*hr)	C_{max} (μM)	C_{12h} (nM)	T_{max}* (hr)*	$t_{1/2}$ (hr)	CL/F (L/h)
1	11	379.6 ± 94.4	15.7 ± 22.4	4.0 ± 6.0	332.6 ± 347	1.0 ± 1.8	3.9 ± 3.6	54.4 ± 56.8
2a	11	400	15.8 ± 36.2	4.8 ± 11.8	246.1 ± 1982.1	2.0 ± 0.9	3.5 ± 1.4	56.8 ± 161.4
2b	10	222.9 ± 58.7	22.6 ± 7.9	10.5 ± 6.4	129.6 ± 155.1	0.5 ± 0.2	3.4 ± 4.2	22.2 ± 8.9
3	12	87.5 ± 22.5	17.9 ± 12.5	9.7 ± 6.6	71.2 ± 49.3	1.0 ± 1.3	3.3 ± 3.2	10.9 ± 10.1

*Median value

Significant intersubject PK variability was observed across all cohorts, but it was higher in subjects using poloxamer tablets compared to chewable tablets under fasting conditions (see table below).

Table 5 Inter-subject PK variability of raltegravir per cohort in Stage 1 (period of intensive PK sampling). Subjects received the recommended final dose of raltegravir using either poloxamer tablets or chewable tablets under fasting conditions.

			C_{12h}			AUC_{0-12h}		
Cohort	N	Formulation	GM (μM)	Median (Range) (nM)	CV%	GM (μM*hr)	Median (Range) (μM*hr)	CV%
1	11	Poloxamer	332.6	309.6 (58.7-1183.3)	78.3	15.7	16.7 (4.6-78.6)	97.6
2a	11	Poloxamer	246.1	241.9 (85.9-6815.7)	220.6	15.8	15.1 (1.6-111.1)	120.4
2b	10	Chewable	129.6	97.7 (64.7-456.8)	87.6	22.6	23.8 (12.8-40.6)	33.6
3	12	Chewable	71.2	80.6 (6.9-185.9)	55.5	17.9	16.4 (5.4-43.7)	58.6
*Adults	6	Poloxamer	141.7	162.4 (65.7-265.5)	212%	14.3	18.5 (3.8-28.8)	-

*Values obtained from trial P004 evaluating efficacy, safety, and tolerability of monotherapy raltegravir 400 mg BID administered for 10 days to treatment naive HIV-infected subjects.

The figures below display individual concentration-time profiles of raltegravir across all cohorts for subjects receiving the final recommended dose of raltegravir using poloxamer tablets (left figure) versus chewable tablets (right

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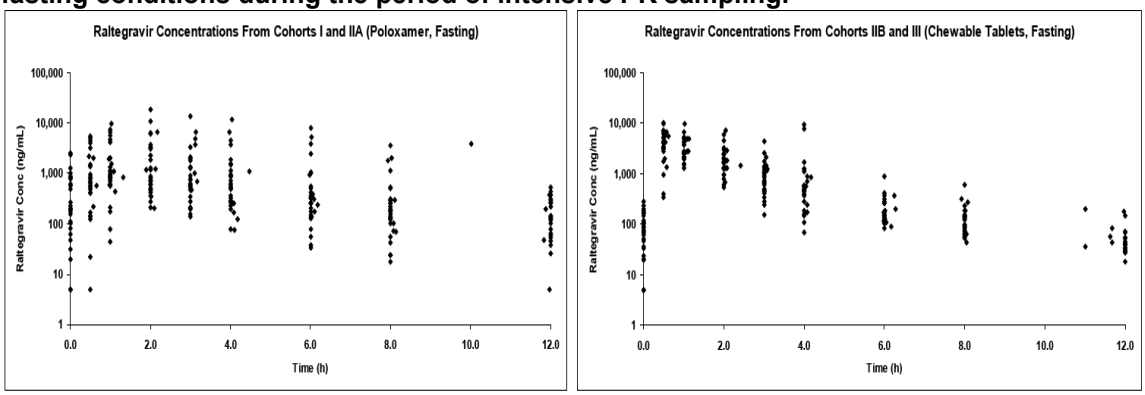
figure). Intersubject PK variability was lower in subjects receiving ethylcellulose chewable tablets.

Figure 1 Raltegravir steady state concentration-time profiles collected from subjects receiving final dose raltegravir using poloxamer (left) and chewable (right) tablets under fasting conditions during the period of intensive PK sampling.



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Pharmacokinetics parameters of raltegravir following administration of final recommended doses for 24 weeks (Stage 2).

In Stage 2, all subjects underwent sparse blood sampling at Weeks 4, 8, 12, and 24 to evaluate steady-state concentrations of raltegravir, including 95 subjects who received the final proposed doses for the first 24 weeks of treatment in Stage 2. Sparse PK data were used to determine the following values for a PK/PD analysis conducted in all cohorts: C_{all} (geometric mean of all sparse concentrations for each subject, regardless of time), C_{12h} (geometric mean of all concentrations collected at 12 ± 2 hours post dose), and C_{min} (minimum trough concentration for each subject, regardless of collection time). These are the same parameters used in the PK/PD analyses performed in adults in the original NDA approval.

The Applicant used two methods to analyze sparse PK data: a statistical summary and a popPK model. Data collected from Cohorts 1 and 2a showed high intrasubject PK variability, which precluded the development of a popPK model. Thus, sparse PK data from Cohorts 1 and 2a were summarized only with a statistical approach, as described above. Conversely, intrasubject PK variability in subjects using chewable tablets was lower than variability observed in subjects receiving poloxamer tablets. Therefore, PK data collected from Cohorts 2b and 3 were analyzed using a popPK model, including all intensive PK data from Stage 1 and sparse samples from Stage 2. Results from both methods are summarized below.

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Table 6 Summary of geometric mean (CV%) PK values calculated using a statistical approach (all cohorts) and a population PK model (Cohorts 2b and 3 only). Sparse PK data were derived from subjects in Stage 2 receiving the final dose of raltegravir for 24 weeks in combination with optimized background HIV therapy (OBT).

	Statistical summary		Population PK		
Cohort	N*	GM C_{12h} (nM) (%CV)	N	GM C_{12h} (nM) (%CV)	GM AUC_{12h} (uM*hr) (%CV)
1	53	225 (175)	-	NA	NA
2a	2	558 (93)	-	NA	NA
2b	12	108 (101)	13	244 (89)	25.3 (23)
3	19	130 (161)	20	157 (176)	19.7 (75)

NA= not available.
*For the Statistical summary, the table is missing five subjects from Cohort 1, two subjects from Cohort 2a, one subject from Cohort 2b, and one subject from Cohort 3. The missing subjects in Cohorts 2b and 3 were included in the population PK analysis. The Sponsor did not provide a rationale for the discrepancy in subject numbers.

Overall, all cohorts achieved the predefined mean C_{12h} target (>33 nM) while receiving raltegravir at final selected doses for 24 weeks. Median raltegravir C_{12h} values in treatment-experienced adults in the two Phase 3 trials were 262 and 281 nM, with a range of 12 – 9151 nM. The popPK model showed that subjects receiving chewable tablets of raltegravir also achieved target $AUC_{0\text{-}12h}$ values (14 to 25 µM*hr). These results suggest that final recommended doses of raltegravir deliver adequate exposures in pediatrics compared to adults.

Summary of results from exposure-response analyses conducted using data from subjects receiving raltegravir final recommended doses for 24 weeks (Stage 2).

In the original NDA submission, raltegravir displayed no clinically meaningful difference in virologic success rates across a wide range of C_{12h} values measured in treatment-experienced adults receiving 400 mg BID. Within the concentration range studied, the virologic success rate was similar (77%) for subjects with lower C_{12h} values (76 nM) compared to those with higher C_{12h} values (1085 nM) (see figure below).

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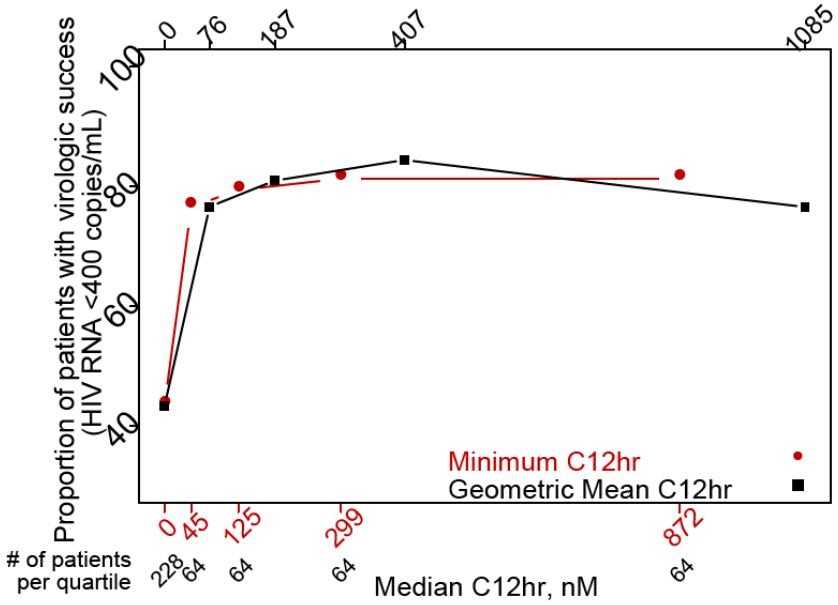
Figure 2 Relationship between C_{12h} and virologic success defined as proportion of subjects achieving HIV RNA <400 copies/mL. C_{12h}=0 represents placebo-treated subjects; raltegravir-treated subjects were divided into four C_{12h} quartiles. A similar trend was observed with subjects achieving HIV RNA <50 copies/mL (not shown).



In this submission, the Applicant explored associations between raltegravir exposures and virologic success using pediatric data. Initial results from an exposure-response analysis suggested a statistically significant ($p<0.05$) association between raltegravir concentrations (C_{all}, GM C_{12h}) and composite virologic success at Week 24 across all cohorts. However, analysis of exposure-response relationships per formulation revealed a statistical significant association only for Cohorts 1 and 2a receiving poloxamer tablets (see table below). As there were only 4 subjects in Cohort 2a in the final PK/PD analysis, the finding is largely driven by Cohort 1.

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Table 7 Population PK parameters as a predictor for antiretroviral responses across all cohorts receiving final dose of raltegravir + OBT for 24 weeks. An odds ratio >1 indicates a probable association between PK and efficacy. A p-value <0.05 indicates statistically significance.

	n[§]	N[§]	Odds Ratio (95% CI)[†]	p-Value[†]
Patients in all four Cohorts (I, IIA, IIB & III)				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	63	85	3.094 (1.110, 8.629)	0.031
Geo Mean of All Observed Conc. (nM) from Sparse PK data	68	94	2.781 (1.145, 6.750)	0.024
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	47	85	4.340 (1.674, 11.256)	0.003
Geo Mean of All Observed Conc. (nM) from Sparse PK data	51	94	2.934 (1.286, 6.693)	0.011
Patients in Cohorts I & IIA only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	41	54	8.668 (1.729, 43.455)	0.009
Geo Mean of All Observed Conc. (nM) from Sparse PK data	44	61	3.896 (1.284, 11.817)	0.016
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	32	54	16.106 (2.998, 86.514)	0.001
Geo Mean of All Observed Conc. (nM) from Sparse PK data	34	61	4.365 (1.457, 13.081)	0.008
Patients in Cohorts IIB & III only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	22	31	0.326 (0.046, 2.288)	0.260
Geo Mean of All Observed Conc. (nM) from Sparse PK data	24	33	1.642 (0.291, 9.248)	0.574
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	15	31	0.763 (0.170, 3.421)	0.724
Geo Mean of All Observed Conc. (nM) from Sparse PK data	17	33	1.580 (0.395, 6.315)	0.517

[†] Logistic regression with PK parameters (in $\log_{10}$ scale) and following covariates: baseline HIV RNA ($\log_{10}$ copies/mL).

[§] N: number of patients with both PK and efficacy data. n: number of patients (out of N) with events.

Suspecting medication non-compliance as a possible cause for the initial PK/PD association, the Applicant repeated the exposure-response analysis by excluding subjects with ≥2 plasma samples BLOQ across all cohorts. Once again, results from the second analysis identified a statistically significant association between GM C_{12h} and proportion of subjects achieving HIV RNA <50 copies/mL, but only in Cohorts 1 and 2a (see figure below).

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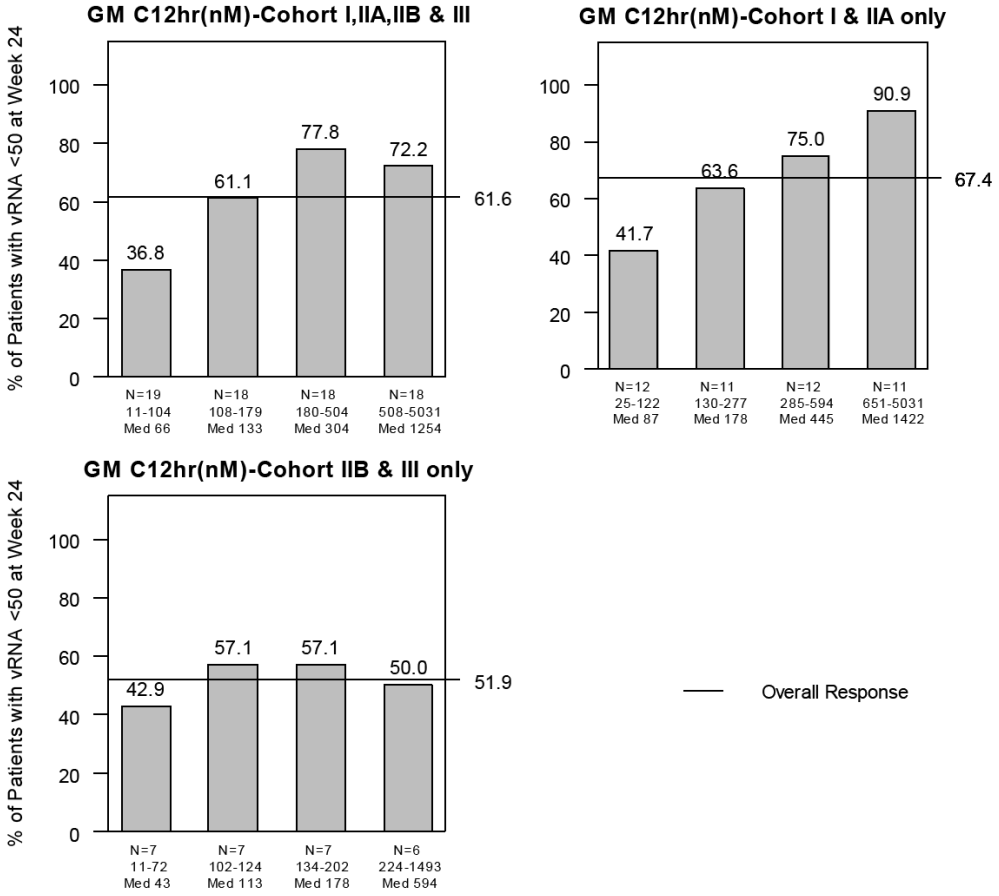
Figure 3 Proportion (%) of subjects with HIV RNA <50 copies/mL plotted against four quartiles of GM C_{12h}. Subjects received final dose of raltegravir in combination with OBT for 24 weeks. The analysis excluded subjects with ≥2 plasma samples BLOQ.



The Applicant did not provide a rationale for this exposure-response association, but speculated the association may be due to medication non-compliance. A review of pill count data suggested that subjects with samples BLOQ were likely to be medication non-compliant; however, the database was difficult to interpret due to missing data. The Applicant tested for development of viral resistance to raltegravir in blood samples obtained from subjects who failed to achieve HIV RNA <400 copies/mL at week 24. However, none of these subjects had raltegravir-associated mutations. Lastly, the Applicant conducted a Receiver Operating Characteristic (ROC) analysis to define a sensitive and specific threshold for raltegravir C_{12h} that would predict virologic success at week 24. Yet, the ROC analysis failed to identify a raltegravir C_{12h} threshold. The median C_{12h} value in the lowest exposure quartile in Cohorts 1 and 2a (87 nM) is higher than the lowest quartile observed in adults (76 nM, refer to figure 2). It should be noted, in the analysis conducted in adults BLOQ values were treated as missing, whereas the current analysis assigns samples BLOQ a value of 5 nM (1/2 x LLOQ).

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Similar to the Applicant's analysis, the Office of Clinical Pharmacology (OCP) reviewer compared virologic success rates at week 24 vs. raltegravir GM C_{12h} in Cohorts 1 and 2a, but included only subjects without any BLOQ samples. When excluding subjects with ≥1 BLOQ samples from the analysis, the exposure-response association largely disappeared, except for the lowest quartile. Subjects in the lowest raltegravir GM $C_{12h,}$ quartile, with individual GM C_{12h} concentrations ≤178, had the lowest virologic success rates in Cohorts 1 and 2a. Results suggest that medication non-compliance may have been a factor for the exposure-response relationship observed in the Applicant's analysis.

Despite results from the Applicant's exposure-response analysis, the OCP reviewer still supports the final recommended doses of raltegravir in pediatric subjects, as proposed by the Applicant. Subjects in Cohorts 1 and 2a receiving raltegravir 400 mg BID using poloxamer tablets for 24 weeks, in combination with OBT, achieved virologic success rates (~55 and 50%) similar to those observed in adults (55%). Moreover, mean $AUC_{0\text{-}12h}$ and C_{12h} values observed in Cohorts 1 and 2a during Stage 1 were comparable to those observed in adults receiving raltegravir 400 mg BID.

Discussion and Conclusions

Based on results from trial P1066, the following conclusions can be made regarding raltegravir dosing in pediatrics:

- The final recommended doses of raltegravir for children and adolescents using poloxamer and chewable tablets delivered a range of exposures similar to those observed in adults receiving raltegravir 400 mg BID using poloxamer tablets.

- Individual and composite mean virologic success rates at week 24 observed across all pediatric cohorts were similar to virologic success rates observed in treatment-experienced adults at week 96.

- A statistically significant exposure-response relationship between raltegravir GM C_{12h} values and proportion of subjects achieving HIV RNA <50 copies/mL was observed in Cohorts 1 and 2a receiving poloxamer tablets. The exposure-response relationship is not fully understood, but the Applicant believes it may be due to medication non-compliance. Nevertheless, the exposure-response relationship does not affect our overall conclusion that the final pediatric doses of raltegravir are adequate given that virologic success rates in pediatrics were similar to those observed in adults.

- Overall, the final doses of raltegravir in pediatrics deliver comparable PK, safety, and efficacy relative to adults.

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Trial 068

This Phase 1 trial compared the relative bioavailability of raltegravir delivered using poloxamer tablets (reference) and ethylcellulose chewable tablets (test). The trial also evaluated an oral granule formulation of raltegravir; however, this review will not discuss results from the oral granule formulation.

The trial had an open-label, three-period, randomized, cross-over design. Twelve subjects received single doses of raltegravir 400 mg delivered as poloxamer tablets or ethylcellulose chewable tablets in three separate periods under fasting conditions. A third period evaluated the effect of a high fat meal on the pharmacokinetics of raltegravir delivered as chewable tablets.

Trial results revealed that raltegravir chewable tablets were not bioequivalent to reference poloxamer tablets. Mean raltegravir $AUC_{0\text{-}inf}$ and C_{max} values were 78% and 222% higher with chewable tablets compared to poloxamer tablets following a single 400 mg dose. On the other hand, raltegravir C_{12h} values were similar for both formulations. The table below summarizes statistical results for poloxamer and chewable tablets administered under fasting conditions.

Table 8 Summary statistics of plasma PK following single dose 400 mg of raltegravir poloxamer tablets and chewable tablets under fasting conditions in healthy adult subjects.

PK parameter (units)	N	Adult tablet Geometric mean	Chewable tablet Geometric mean	Comparison	GMR (90% CI)
C_{12h} (nM)	12	149	134	Chewable/Poloxamer	0.90 (0.70, 1.18)
$AUC_{0\text{-}inf}$ (μM*hr)	12	19.2	34.2	Chewable/Poloxamer	1.78 (1.47, 2.15)
C_{max} (μM)	12	5.0	16.1	Chewable/Poloxamer	3.22 (2.37, 4.38)
Median T_{max} (hr)	12	4.0 (range 1 to 6)	0.5 (range 0.5 to 1.5)	--	--

When raltegravir chewable tablets were administered with a high fat meal, the median rate of raltegravir's absorption (T_{max}) decreased, delaying the T_{max} slightly, the mean C_{max} decreased, and the extent of absorption ($AUC_{0\text{-}inf}$) was unchanged relative to fasting conditions. Conversely, food substantially increased mean C_{12h} values relative to fasting conditions. The table below summarizes statistical results for chewable tablets administered under fed or fasting conditions.

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Table 9 Summary statistics of plasma PK following single dose 400 mg raltegravir chewable tablets under fasting and fed conditions in healthy adult subjects.

PK parameter (units)	N	Fasting Geometric mean	Fed Geometric mean	Comparison	GMR (90% CI)
C_{12h} (nM)	12	134	387	Fed/fasting	2.88 (2.21, 3.75)
$AUC_{0\text{-}inf}$ (μM*hr)	12	34.2	32.3	Fed/fasting	0.94 (0.78, 1.14)
C_{max} (μM)	12	16.1	6.14	Fed/fasting	0.38 (0.28, 0.52)
T_{max} (hr)[1]	12	0.5	1.0	-------	

[1]Median values presented for T_{max}.

Discussion and Conclusions

Based on results from trial P068, the following conclusions can be made regarding raltegravir exposures delivered using poloxamer and ethylcellulose chewable tablets:

- Raltegravir poloxamer and chewable tablets are not bioequivalent and should not be used interchangeably at the same dose in a clinical setting. Chewable tablets deliver higher raltegravir exposures ($AUC_{0\text{-}inf}$ and C_{max}) relative to commercially available poloxamer tablets under fasting conditions.

- Raltegravir chewable tablets can be administered with or without food. Food increases C_{12h} concentrations but does not affect the overall exposure ($AUC_{0\text{-}inf}$) of raltegravir. Raltegravir C_{12h} and AUC_{12h} are suspected to be the primary parameters responsible for antiviral efficacy. Conversely, food decreased the C_{max} of raltegravir by 62% relative to fasting conditions. In the original NDA for raltegravir, a similar food effect trend was observed: C_{max} decreased by 34% under fed conditions with the poloxamer tablets.

- Dr. Arzu Selen, the FDA Biopharmaceutics reviewer for this submission, confirmed that both chewable tablet strengths (25 mg and 100 mg) may be used interchangeably. For example, four-25 mg tablets may be used instead of one-100 mg tablet to deliver a dose of 100 mg. (b) (4) . The color and flavor ratios vary, but these components are not expected to affect the oral bioavailability of raltegravir.

- Dr. Selen also confirmed that pediatric patients may swallow the chewable tablets whole, instead of chewing them based on results from *in vitro* dissolution experiments (Q= (b) (4) in 15 minutes; Q+5%= (b) (4)). In P1066, three subjects reported that chewable tablets had an unpleasant taste, and consequently, swallowed them whole. One subject had a raltegravir steady

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state C_{12h} concentration (108 nM) that was comparable to C_{12h} concentrations (83.5-176.4 nM) observed in other subjects in Cohort 2b, receiving the same raltegravir dose, who chewed the tablets. This finding suggests that raltegravir PK parameters are similar when chewing or swallowing tablets; although one may expect raltegravir T_{max} and C_{max} to be faster and higher when chewing versus swallowing completely.

2. Labeling Recommendations

The Clinical Pharmacology reviewer recommends the following labeling changes shown in blue and edits in track changes. This document only shows edited sections in the proposed label for raltegravir.

Original Language from Applicant	OCP Proposed changes
(b) (4)	

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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(b) (4)

3. Appendices

3.1 individual Trial Reviews

3.1.1 Trial P1066 (also known as P022 or IMPAACT)

A Phase I/II, multicenter, open-label, noncomparative trial of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to evaluate safety, tolerability, pharmacokinetics (PK), and antiretroviral activity of raltegravir (Isentress™, MK-0518) in HIV-1 infected infants, children, and adolescent.

Trial Period

Trial initiation: September 14, 2007
Data cut-off: February 14, 2011 (trial is ongoing)

Trial sites

The trial was conducted in multiple sites located in the US (41), Brazil (8), South Africa (4), Botswana (2), and Argentina (1).

Trial Rationale

HIV-infected children, particularly those who develop viral resistance or toxicities, have limited antiretroviral (ARV) treatment options. As with adults, ARV therapy

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with at least three drugs is recommended for children to prevent viral resistance. With over 30 different ARVs in the marketplace, adults have a variety of treatment options. Conversely, children have limited treatment options because many ARVs are unapproved for use in children, or are unavailable in appropriate formulations. Thus, Merck has developed a chewable tablet of raltegravir suitable for children, and seeks an indication for raltegravir in this population.

Trial Objectives

Primary:

- Evaluate short-term safety, tolerability, and PK of raltegravir in combination with ARV background therapy in infants, children, and adolescents (Stage 1).

- Evaluate long-term safety and tolerability of raltegravir using selected final dose in combination with optimized background therapy (OBT) over 24 weeks in infants, children, and adolescents (Stage 2).

Secondary:

- Evaluate safety and tolerability of raltegravir chronic dosing using the selected final dose in combination with OBT, as assessed by reviewing safety data accumulated over 48 weeks.

- Evaluate antiretroviral activity of raltegravir using selected final doses in combination with OBT, as assessed by change in HIV RNA from baseline over 24 and 48 weeks of treatment.

- Evaluate immunological activity of raltegravir using selected final dose in combination with OBT, as measured by changes in CD4 cell count and percent from baseline over 24 and 48 weeks of treatment.

- Describe pediatric raltegravir exposure over time, using a population PK modeling approach.

- Develop and implement a raltegravir dried blood spot (DBS) method for PK evaluations in the younger cohorts of P1066.

Tertiary:

- Evaluate long-term safety and efficacy of raltegravir in subjects treated for >48 weeks.

Trial Population

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One hundred and twenty six subjects infected with HIV-1, at the time of data cut-off.

Trial Design

P1066 is an ongoing multi-center, open-label, noncomparative trial in HIV-1 infected children and adolescents ranging from ≥4 weeks to <19 years of age who failed previous therapy with at least one ARV medication. The current submission contains data from children ≥2 to <19 years of age who received raltegravir using poloxamer or chewable tablets in combination with OBT. The trial is also testing an oral granule formulation for children ≥4 weeks to <2 years of age. However, oral granule formulation data (b) (4) will not be discussed in this review. The trial is enrolling six age cohorts as follows:

Cohort 1: ≥12 to ≤18 years of age received poloxamer tablets.

Cohort 2a: ≥6 to ≤11 years of age received poloxamer tablets.

Cohort 2b: ≥6 to ≤11 years of age received chewable tablets.

Cohort 3: ≥2 to ≤5 years of age received chewable tablets.

Cohort 4: ≥6 months (defined as 180 days) to <2 years of age received oral granules for suspension.

Cohort 5: ≥4 weeks (defined as 30 days) to <6 months of age received oral granules for suspension.

The trial was conducted in two sequential stages:

Stage 1 was a dose-finding period enrolling 58 subjects across Cohorts 1, 2a, 2b, and 3. Each age cohort was divided in two parts: a 'mini-cohort' and a 'full-cohort'. The mini-cohort was comprised of 4 subjects. These subjects received raltegravir in combination with their current background ARVs. The full cohort (n=10 to 12) was enrolled only if the dose of raltegravir was safe and met the predefined PK targets for $AUC_{0\text{-}24h}$ and C_{12h} in the mini-cohort. This dosing scheme was repeated until raltegravir final selected doses were identified in all age cohorts. Subjects completing Stage 1 rolled into Stage 2 to receive long-term treatment with final selected doses of raltegravir.

Stage 2 evaluated long-term safety and efficacy of final recommended doses of raltegravir in combination with OBT administered for 48 weeks. Subjects who completed 48 weeks of raltegravir treatment may have continued receiving

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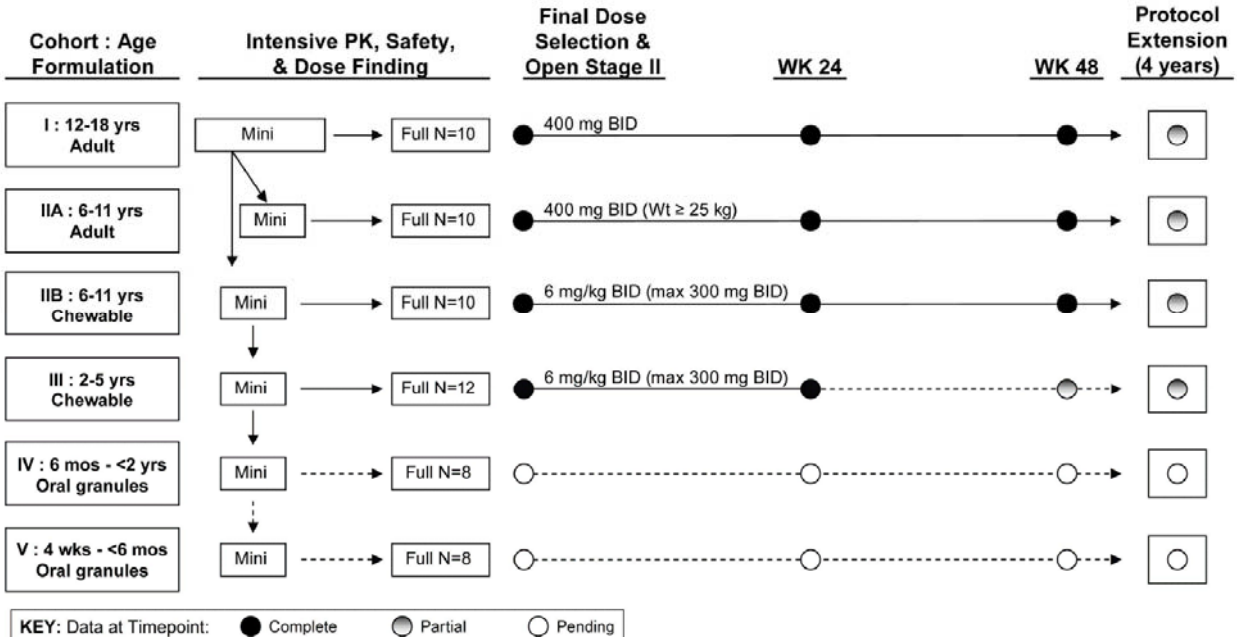
raltegravir for an additional 4 years via an extension protocol. The design of P1066 is displayed below.

Figure 4 Trial design



Subjects in Stage 1 received raltegravir in combination with prior stable ARV regimen. A stable ARV regimen was defined as 1) subjects receiving unchanged therapeutic regimen for at least 12 weeks, or 2) treatment experienced subjects receiving no treatment for ≥4 weeks prior to entry. ARV treatment was optimized in subjects after completing intensive PK sampling in Stage 1.

In contrast, subjects in Stage 2 optimized their ARV regimens before or concurrently while receiving the final selected dose of raltegravir for 48 weeks. Once the ARV regimen was optimized, additional changes to the ARV regimen were not allowed in either Stage 1 or 2, unless 1) ARV substitution was within the same drug class, 2) ARV substitution was across drug class due to documented toxicity, 3) discontinuation of a background ARV, or 4) formula substitutions.

Key inclusion/exclusion criteria

Inclusion

- Subjects between ≥ 4 weeks to <19 years of age.
- Documented HIV-1 infection.
- Receiving stable ARV for at least 12 weeks, or be treatment experienced but not receiving treatment for ≥4 weeks prior to trial entry. Dose adjustments for

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growth were permitted with investigator approval. Formulation changes and within drug class substitutions were permitted within the last 12 weeks of treatment.

- Subjects were required to have HIV RNA ≤1 log drop within 12 weeks of receiving stable ARV treatment, or HIV RNA ≥25,000 copies/mL at screening. Note: These criteria did not apply to treatment-experienced subjects who had not received ARV therapy for ≥4 weeks prior to entry.
- HIV RNA ≥ 1,000 copies/mL at screening.
- Female subjects of childbearing potential and sexually active were required to use two methods of birth control during the trial and for 3 months after stopping raltegravir. Acceptable methods included condoms, diaphragms, cervical caps with spermicide (excluding nonoxynol-9), intrauterine devices, and other barriers. Condoms were recommended because of their use in contraception and prevention of HIV transmission. Hormonal contraception alone was not acceptable (e.g. oral, injections, or slow release inserts).

Exclusion

- Abnormal blood chemistry before trial entry, including neutrophil counts, hemoglobin, platelets, AST, ALT, lipase, or serum creatinine.
- Use of atazanavir, tenofovir, or tipranavir in Stage 1.
- Hyperbilirubinemia ≥ Grade 4 within 30 days prior to trial entry (only applicable to subjects enrolling in Stage 2 whose stable background regimen included atazanavir.
- CDC Stage C criteria or opportunistic or bacterial infection diagnosed within 30 days prior to screening and not considered clinically stable.
- Subjects who were pregnant or breastfeeding.
- Prohibited medications listed below in the Concomitant Medication section.

Rationale for Dose Selection

The approach for raltegravir dose selection in each cohort was to determine a pediatric dose that would approximate adult exposures achieved with 400 mg BID dose using poloxamer tablets. The target exposure for each cohort was a geometric mean (GM) $AUC_{0\text{-}12h}$ between 14 to 25 μM*hr, with a concurrent goal that GM C_{12h} exceed 33 nM (IC_{95}). For safety considerations, the maximum individual $AUC_{0\text{-}12h}$ was defined as <45 μM*hr, which represents half the raltegravir $AUC_{0\text{-}24h}$ after single doses of 1600 mg given in Phase 1 clinical trials of raltegravir.

Pediatric subjects received raltegravir in a weight-based manner. The first dose of raltegravir in Cohort 1 was ~6 mg/kg BID. This weight-based dose approximates a 400 mg BID dose administered to a 70-kg adult. If the raltegravir exposure data (for a mini cohort or full cohort) were not acceptable, the dose was modified using the linear-dose adjustment formula below.

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$$\frac{\text{Current RAL Dose}}{\text{Geometric Mean RAL AUC}_{12}} = \frac{\text{New RAL Dose}}{14\ \mu\text{Mxh AUC}_{12}\ \text{Target}}$$

Upon selecting the final dose of raltegravir for each cohort, subjects were rolled into Stage 2. In Stage 2, subjects received 48 weeks of raltegravir final dose in combination with OBT.

Investigational Product

Subjects in Cohorts 1 and 2a received poloxamer film-coated adult tablets twice daily. The tablets were available in three strengths: 100, 200, and 400 mg. The 100 and 200 mg tablets were phased out during evaluation.

Subjects in Cohorts 2b and 3 received ethylcellulose chewable tablets twice daily. The tablets were initially available in three strengths: 25, 50, and 100 mg. (b) (4)

Subjects who crossed the age boundary for formulation were expected to receive their initial raltegravir formulation for at least 48 weeks with their dose increased appropriately for weight increases. After 48 weeks of treatment, subjects were allowed to switch formulations (e.g. from chewable tablets to adult tablets).

Drug Administration

Subjects received open-label raltegravir in combination with ARV according to their respective cohorts:

- Subjects in Cohorts 1 and 2a initially received adult tablets twice daily under non-fasting conditions in Stage 1. Initial PK data collected in these cohorts was highly variable. Food was suspected to be the source of PK variability. The protocol was amended to ensure raltegravir was administered under fasting conditions on days of intensive PK sampling. Liquids, including milk and juice, were allowed up to four hours before dosing. Water was allowed as desired. Subjects were allowed to ingest a light meal (not high fat) two hours after raltegravir dosing. On non-PK sampling days, subjects were allowed to ingest raltegravir without regard to food.

- Subjects in Cohorts 2b and 3 received chewable tablets twice daily without regard to food, except on intensive PK sampling days when doses were given under fasting conditions. Subjects were instructed to chew raltegravir tablets before swallowing them.

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Concomitant medications

Use of the following medications was prohibited during the trial:

- Phenobarbital
- Phenytoin
- Rifampin
- Rifabutin (allowed in Stage 2, but not during intensive PK sampling in Stage 1)
- Atazanavir (allowed in Stage 2 only)
- Tenofovir disoproxil fumarate (allowed in Stage 2 only)
- Tipranavir (allowed in Stage 2 only)
- Systemic immunosuppressive medications

Collection of plasma samples for raltegravir PK

Intensive PK sampling (Stage 1) from Cohorts 1, 2a, 2b, and 3

Plasma samples were collected at predose, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post dose between 5 and 12 days after initiating raltegravir dosing. Repeat intensive PK visits occurred between days 7 and 14 following dose adjustment, if required. Intensive PK visits were scheduled for witnessed dosing approximately 12 hours (11 to 13 h) after the previous dose.

Sparse PK sampling (Stage 2) from Cohorts 1, 2a, 2b, and 3

Plasma samples were collected in all subjects at:

- Week 4 (one sample between 10 and 14 hours post dose)
- Week 8 (two samples separated by 2 hours between 0.5 and 6 hours post dose)
- Week 12 (one sample between 10 and 14 hours post dose)
- Week 24 (two samples separated by 2 hours between 6 and 12 hours post dose)

Collection of blood samples for efficacy evaluation

P1066 was not designed or powered to demonstrate efficacy, but efficacy measures included both antiviral (HIV RNA) and immunologic effects (CD4 cells), as follows:

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- Screening and trial entry.
- Weeks 1, 4, 8, 12, 24, 36, and 48.
- Safety visit for Stage 1 subjects whose dose was increased to Stage 2 dose.
- Follow-up visit at 14-day post therapy.
- Early discontinuation visit.
- Every 4 months (± 6 weeks) for 5 years after completion of Stage 2 for subjects who continue trial-provided raltegravir. For subjects who discontinued trial-provided raltegravir, HIV RNA will be measured every 12 months for 5 years after initial raltegravir exposure.

Blood samples for evaluating viral resistance during treatment with raltegravir and ARV

Blood samples were collected at:
- Screening
- Weeks 12, 24, 36, and 48

Analytical plan for PK data collected in Cohorts 1 – 3.

Intensive PK sampling (Stage 1)

PK data were analyzed using non-compartmental analysis. The PK parameters of interest were $AUC_{0\text{-}12h}$, C_{max}, T_{max}, and C_{12h}. $AUC_{0\text{-}12h}$ was determined using a linear and logarithmic trapezoidal method, while C_{max} and T_{max} were observed directly from concentration-time PK profiles of raltegravir.

Sparse PK sampling (Stages 1 and 2)

PK data collected from Stages 1 and 2 were analyzed for Cohorts 2b and 3 using a population PK model to determine if covariates such as age, weight, and sex had an effect on the PK of raltegravir in pediatric subjects.

Sparse PK data were also analyzed to determine C_{min} (minimum trough concentration for each subject, regardless of collection time), GM C_{12h} (geometric mean of all concentrations collected at 12 ± 2 hours post dose), and C_{all} (geometric mean of all sparse concentrations for each subject, regardless of time) across all cohorts at the final dose of raltegravir. A PK/PD model evaluated potential associations between C_{min}, GM C_{12h}, and C_{all} and antiretroviral efficacy defined as:

- Achieving at least 1 log drop in HIV RNA or HIV RNA <400 copies/mL at Week 24.
- Achieving HIV RNA <50 copies/mL at Week 24.

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Statistical analyses

PK data analysis

The primary non-compartmental analysis results were reported with descriptive statistics for each cohort at each dose tested.

Logistic regression analyses were conducted using the PK endpoints GM C_{12h}, C_{all}, and the PD endpoints ≥1 log drop or HIV RNA <400 copies/mL and HIV RNA <50 copies/mL to evaluate potential PK/PD associations for all subjects receiving both formulations of raltegravir.

A Receiver Operating Characteristic (ROC) analysis was performed to assess if a single threshold value of raltegravir GM C_{12h} could predict, with high sensitivity and specificity, a subject achieving HIV RNA <50 copies/mL at week 24.

Efficacy analysis

The efficacy analyses included evaluations of antiretroviral activity and immunological activity at weeks 24 (all cohorts) and 48 (Cohorts 1, 2a, and 2b) for the final recommended dose of raltegravir in combination with OBT. Both analyses included the proportion of subjects achieving virologic success and mean change from baseline in CD4 cell count and CD4% bounded by 95% confidence intervals.

Logistic regression models were conducted to identify variables predicting virologic success. Variables included gender, ethnicity, baseline HIV RNA (≤50,000 copies/mL or >50,000 copies/mL), baseline CD4 cell count (≤200 cells/mm^3 or >200 cells/mm^3), viral subtype (clade B or non-clade B), and previous antiretroviral drug classes used.

Trial results

Bioanalytical method

The method and bioanalysis of raltegravir is acceptable. The (b) (4) analyzed all plasma samples from P1066 using a validated LC-MS/MS method.

Plasma samples of raltegravir were stable during storage and bioanalysis. When stored, plasma samples remained at -80°C for less than 19 months--the long-term stability period for raltegravir samples. During bioanalysis, plasma samples

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were thawed and remained at room temperature up to 72 hours. A short-term stability study showed no raltegravir degradation during bioanalysis.

The calibration standards and quality control (QC) samples were adequate. The calibration curve was linear over a range of 1 to 3000 ng/mL (Mean r^2=0.9992). The mean relative error (% deviation) ranged from -3.3 to 4.2%. The coefficient of variation (%CV) ranged from 0.6 to 2.9%. The precision for quality control samples, low QC (3 ng/mL), mid QC (540 ng/mL), and high QC (2700 ng/mL), ranged from 1.3 to 7.5%. The accuracy ranged from -7.4 to 11.5%.

Demographics

The trial population adequately represented females and minorities. Most subjects (67%) had previously received ≥3 classes of ARVs. The table below summarizes baseline characteristics for subjects who received the selected final dose of raltegravir (n=96).

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Table 10 Baseline characteristics of subjects by cohort; final dose population

	Cohort I (N=59) n (%)	Cohort IIA (N=4) n (%)	Cohort IIB (N=13) n (%)	Cohort III (N=20) n (%)	Total (N=96) n (%)
Gender					
Male	30 (50.8)	3 (75)	7 (53.8)	7 (35)	47 (49)
Female	29 (49.2)	1 (25)	6 (46.2)	13 (65)	49 (51)
Race					
Black or African American	35 (59.3)	3 (75)	7 (53.8)	12 (60)	57 (59.4)
White	21 (35.6)	1 (25)	6 (46.2)	5 (25)	33 (34.4)
American Indian	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1)
Multi-racial	0 (0)	0 (0)	0 (0)	1 (5)	1 (1)
Unknown	2 (3.4)	0 (0)	0 (0)	2 (10)	4 (4.2)
Ethnicity					
Hispanic or Latino	22 (37.3)	1 (25)	7 (53.8)	8 (40)	38 (39.6)
Not Hispanic or Latino	34 (57.6)	2 (50)	6 (46.2)	9 (45)	51 (53.1)
Unknown	3 (5.1)	1 (25)	0 (0)	3 (15)	7 (7.3)
CDC HIV Clinical Classification					
A	14 (23.7)	2 (50)	6 (46.2)	5 (25)	27 (28.1)
B	24 (40.7)	0 (0)	3 (23.1)	1 (5)	28 (29.2)
C	21 (35.6)	1 (25)	0 (0)	7 (35)	29 (30.2)
N	0 (0)	1 (25)	4 (30.8)	7 (35)	12 (12.5)
Viral Subtype					
Clade B	54 (91.5)	2 (50)	6 (46.2)	7 (35)	69 (71.9)
Non-Clade B[†]	4 (6.8)	2 (50)	7 (53.8)	12 (60)	25 (26)
MISSING	1 (1.7)	0 (0)	0 (0)	1 (5)	2 (2.1)
Number of ARV Classes Previously Used					
0	0 (0)	0 (0)	0 (0)	1 (5)	1 (1)
1	2 (3.4)	0 (0)	0 (0)	2 (10)	4 (4.2)
2	6 (10.2)	2 (50)	7 (53.8)	12 (60)	27 (28.1)
>=3	51 (86.4)	2 (50)	6 (46.2)	5 (25)	64 (66.7)
Patients with Prior NNRTI Use	51 (86.4)	3 (75)	11 (84.6)	10 (50)	75 (78.1)
Patients with Prior PI Use	57 (96.6)	3 (75)	8 (61.5)	12 (60)	80 (83.3)
Baseline Plasma HIV RNA (copies/mL)					
0 - <=4,000	9 (15.3)	1 (25)	1 (7.7)	2 (10)	13 (13.5)
>4,000 - <=50,000	36 (61)	2 (50)	9 (69.2)	11 (55)	58 (60.4)
>50,000 - <=100,000	10 (16.9)	1 (25)	2 (15.4)	4 (20)	17 (17.7)
>100,000	4 (6.8)	0 (0)	1 (7.7)	3 (15)	8 (8.3)
Phenotypic Sensitivity Score (PSS[‡])					
0	3 (5.1)	0 (0)	0 (0)	0 (0)	3 (3.1)
1	11 (18.6)	1 (25)	4 (30.8)	2 (10)	18 (18.8)
2	23 (39)	0 (0)	7 (53.8)	7 (35)	37 (38.5)
>=3	18 (30.5)	2 (50)	1 (7.7)	6 (30)	27 (28.1)
MISSING	4 (6.8)	1 (25)	1 (7.7)	5 (25)	11 (11.5)
Genotypic Sensitivity Score (GSS[‡])					
0	5 (8.5)	0 (0)	0 (0)	0 (0)	5 (5.2)
1	19 (32.2)	1 (25)	6 (46.2)	2 (10)	28 (29.2)
2	19 (32.2)	2 (50)	6 (46.2)	10 (50)	37 (38.5)
>=3	15 (25.4)	1 (25)	1 (7.7)	7 (35)	24 (25)
MISSING	1 (1.7)	0 (0)	0 (0)	1 (5)	2 (2.1)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.
[†]Non-Clade B subtypes reported include: A1, AG, C, R12 and R31.
[‡]The Genotypic Sensitivity Score (GSS) and Phenotypic Sensitivity score (PSS) were defined as the total number of ARVs in OBT to which the patient's viral isolate showed genotypic/phenotypic sensitivity, based upon resistance tests performed prestudy (or at screening). If no resistance results were available for certain drugs, they will be scored as one active drug in the GSS and PSS if the patient had no prior history of use, and considered as not active
if the patient had used it in the past. Scoring does not include Raltegravir.

Concomitant medications

Raltegravir was administered in combination with other antiretroviral agents. In Stage 1, subjects maintained their prior stable ARV therapy (except atazanavir, tenofovir, or tipranavir) until intensive PK sampling was completed, and only until

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the end of intensive PK sampling did subjects optimize their ARV therapy. Subjects in Stage 2 had their ARV regimen optimized concurrently while receiving raltegravir at the final dose. The following table displays ARV therapy used during Stage 2.

Table 11 Number (%) of subjects with specific concomitant antiretroviral therapies by Cohort; (incidence >0% in one or more cohorts); final dose population.

Concomitant Antiretroviral Therapies	Cohort I (N=59) n (%)	Cohort IIA (N=4) n (%)	Cohort IIB (N=13) n (%)	Cohort III (N=20) n (%)	Total (N=96) n (%)
Patients with one or more concomitant antiretroviral therapies	59 (100)	4 (100)	13 (100)	20 (100)	96 (100)
3TC (lamivudine)	14 (23.7)	3 (75)	9 (69.2)	14 (70)	40 (41.7)
ABC (abacavir)	10 (16.9)	1 (25)	2 (15.4)	6 (30)	19 (19.8)
ATV (atazanavir)	3 (5.1)	1 (25)	1 (7.7)	0 (0)	5 (5.2)
D4T (stavudine)	3 (5.1)	1 (25)	0 (0)	4 (20)	8 (8.3)
DDI (didanosine)	9 (15.3)	0 (0)	1 (7.7)	6 (30)	16 (16.7)
DRV (darunavir)	32 (54.2)	0 (0)	2 (15.4)	2 (10)	36 (37.5)
EFV (efavirenz)	6 (10.2)	2 (50)	1 (7.7)	3 (15)	12 (12.5)
ENF (enfuvirtide)	2 (3.4)	0 (0)	0 (0)	0 (0)	2 (2.1)
ETR (etravirine)	18 (30.5)	0 (0)	2 (15.4)	0 (0)	20 (20.8)
FPV (fosamprenavir)	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1)
FTC (emtricitabine)	31 (52.5)	2 (50)	0 (0)	0 (0)	33 (34.4)
LPV/RTV (kaletra)	14 (23.7)	2 (50)	9 (69.2)	14 (70)	39 (40.6)
MVC (maraviroc)	3 (5.1)	0 (0)	0 (0)	0 (0)	3 (3.1)
NVP (nevirapine)	1 (1.7)	1 (25)	0 (0)	2 (10)	4 (4.2)
RTV (ritonavir)	38 (64.4)	1 (25)	2 (15.4)	2 (10)	43 (44.8)
SQV (saquinavir)	2 (3.4)	1 (25)	1 (7.7)	0 (0)	4 (4.2)
TDF (tenofovir)	33 (55.9)	3 (75)	6 (46.2)	3 (15)	45 (46.9)
TPV (tipranavir)	2 (3.4)	0 (0)	0 (0)	0 (0)	2 (2.1)
ZDV (zidovudine)	11 (18.6)	1 (25)	10 (76.9)	10 (50)	32 (33.3)

N = Number of patients in each cohort.
n (%) = Number (percent) of patients in each subcategory.

Results of raltegravir dose finding during Stage 1

<u>Cohort 1 (≥12 years to <19 years of age) receiving raltegravir adult tablets (100, 200 and 400 mg strength tablets)</u>

- First mini cohort (n=4):

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Subjects received raltegravir ~6 mg/kg BID under non-fasting conditions. The initial dose missed the predefined mean PK target (AUC_{0-12h}=14 to 25 μM*hr) by delivering a GM AUC_{0-12h} of 10.4 μM*hr. Investigators increased raltegravir dose to ~8 mg/kg BID.

- Second mini cohort (n=4):

  Subjects received raltegravir ~8 mg/kg BID under non-fasting conditions. The dose met the mean PK target by delivering a GM AUC_{0-12h} of 19.8 μM*hr. Subsequently, investigators enrolled the full cohort.

- First full cohort (non-fasting) (n=10):

  Subjects received raltegravir ~8 mg/kg BID under non-fasting conditions. The dose missed the mean PK target by delivering a GM AUC_{0-12h} of 6.6 μM*hr. There was a discrepancy in PK exposures between the mini cohort and full cohort receiving ~8 mg/kg BID. Investigators believed food may have caused the PK variability. Investigators re-enrolled full cohort 1 with new subjects to receive ~8 mg/kg under fasting conditions.

- Second full cohort (fasting) (n=11 new subjects):

  Subjects received raltegravir ~8 mg/kg BID under fasting conditions. The dose met the mean PK target by delivering a GM AUC_{0-12h} of 15.7 μM*hr. Most (n=8/11) subjects in Cohort 1 received raltegravir 400 mg BID, despite weight-based dosing.

  Investigators noticed that subjects receiving the lowest doses of raltegravir had low AUC_{0-12h} values. Subject 502828E received 200 mg BID and had an AUC_{0-12h} value of 8.1 μM*hr. Conversely, subjects receiving the highest doses had high AUC_{0-12h} values. Subject 670119E received 600 mg BID and had an AUC_{0-12h} value of 78.6 μM*hr. The Sponsor argues these subjects would have achieved target exposures had they received raltegravir 400 mg BID (assuming linear PK).

  *<u>Reviewer's comment</u>: The Sponsor makes a reasonable argument for dosing subjects at 400 mg BID based on the linear PK properties of raltegravir. However, dosing every subject with raltegravir 400 mg BID does not guaranteed that everyone will meet the PK target. For instance, three subjects receiving 400 mg BID had AUC_{0-12h} values below 14 μM*hr. One of these subjects (509863E) had an AUC_{0-12h} value of 4.5 μM*hr. Overall, a mean dose of raltegravir 380 mg BID produced a GM value of 15.7 μM*hr. Thus, it is reasonable to recommend a flat dose of 400 mg BID to all children ranging from ≥12 years to <19 years of age.*

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- The overall dosing recommendation for this age group was raltegravir 400 mg BID using the adult tablets.

Table 12 Statistical summary of raltegravir PK results obtained from Cohort 1 (≥12 to <19 years) in the final dose cohort.

Cohort	Subject	Actual Dose (mg BID)	Weight (kg)	Dose (mg/kg BID)	C_{12h} (nM)	AUC_{12h} (μM*hr)	C_{max} (μM)
Final Cohort (fasting) 8 mg/kg Adult tablet	450381F	400	59.6	6.7	328.3	31.6	10.7
	501307I	400	35.5	11.3	1183.3	21.0	2.9
	502259A	300	29.7	10.1	577.1	7.6	3.1
	502828E	200	20.7	9.7	494.8	8.1	1.3
	503227G	400	39.8	10.1	145.8	16.7	5.3
	509863E	400	37.4	10.7	58.7	4.6	2.0
	650061L	400	56.2	7.1	309.6	6.5	0.8
	670119E	600	60.7	9.9	967.9	78.6	18.3
	670661F	400	58.7	6.8	278.1	46.1	15.0
	8501237C	400	39.8	10.1	301.3	23.8	8.4
	8501372H	400	40.9	9.8	231.3	8.4	1.8
	N	11	11	11	11	11	11
	Mean	390.9	43.6	9.3	443.3	23.0	6.3
	SD	94.4	13.4	1.6	346.9	22.4	6.0
	CV%	24.2	30.8	17.5	78.3	97.6	95.1
	GM	**379.6**	**41.5**	**9.2**	**332.6**	**15.7**	**4.0**

Cohort 2a (≥6 years to <12 years of age) dosed with raltegravir adult tablets

The first mini-cohort 2a was conducted in parallel with Cohort 1. As a result, the initial dose of raltegravir was administered using the adult tablet formulation under non-fasting conditions.

- First mini cohort (n=4):

  Subjects received raltegravir ~8 mg/kg BID under non-fasting conditions. The initial dose missed the predefined mean PK target by delivering a GM AUC_{0-12h} of 8.7 μM*hr. Investigators enrolled a second mini-cohort to receive raltegravir ~8 mg/kg BID under fasting conditions.

- Second mini cohort (n=4 new subjects):

  Subjects received raltegravir ~8 mg/kg BID under fasting conditions. The dose met the mean PK target by delivering a GM AUC_{0-12h} of 15.4 μM*hr. Subsequently, investigators enrolled the full cohort.

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- First full cohort (n=10):

  Subjects received raltegravir ~8 mg/kg BID under fasting conditions. The dose missed the mean PK target by delivering a GM $AUC_{0\text{-}12h}$ of 12.0 μM*hr. Most (6/10) subjects received raltegravir 300 mg BID. Using a similar rationale from Cohort 1, investigators dosed everybody in a second full cohort using raltegravir 400 mg BID under fasting conditions.

- Second full cohort (n=11):

  Subjects received a flat dose of raltegravir 400 mg BID using adult tablets under fasting conditions. The dose met the mean PK target by delivering a GM $AUC_{0\text{-}12h}$ of 15.9 μM*hr.

  Two subjects had 5 to 7-fold higher raltegravir exposures compared to mean cohort values. Subjects 650947F and 730158K had $AUC_{0\text{-}12h}$ values of 88.0 and 111.1 μM*hr, respectively. These subjects weighed less than 25 kg. Assuming weight was responsible for differences in PK exposures; investigators re-dosed the two subjects based on body weight at ~6 mg/kg BID using the chewable tablets under fasting conditions. Their new $AUC_{0\text{-}12h}$ values, 17.6 and 30.4 μM*hr, met the predefined target (The acceptable range for individual $AUC_{0\text{-}12h}$ values ranged from 5 to 45 μM*hr). The Sponsor included these two subjects in their summary of PK results from Cohort 2a; however, the OCP reviewer removed these subjects from the PK summary (Table 14) because the subjects are not considered part of the final dosing recommendation for this age group (because they weighed less than 25 kg).

  Not all subjects weighing <25 kg had high $AUC_{0\text{-}12h}$ values. Subject 650875J (22.7 kg) had a low $AUC_{0\text{-}12h}$ value of 6.26 μM*hr while receiving 400 mg BID using adult tablets. Investigators were unable to re-dose the subject using chewable tablets because the subject weighed >25 kg during the next trial visit.

- The Sponsor recommends children ranging from ≥6 to <12 years of age and weighing ≥25 kg and able to swallow tablets receive 400 mg BID using adult tablets. Children in the same age range weighing <25 kg should receive raltegravir weight-based dosing using the chewable tablets not to exceed 300 mg BID.

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Table 13 Comparison of raltegravir PK results for two subjects who received raltegravir adult tablets (Cohort 2a) and later switched to chewable tablets (Cohort 2b).

Cohort	Subject	Formulation	Actual dose received (mg BID)	Weight (kg)	Dose (mg/kg BID)	C12h (nM)	AUC12h (uM*hr)
2a	650947F	Adult tablet	400	19.6	20.4	6815.7	88.0
2b	650947F	Chewable tablet	125	19.9	6.3	414.0	17.6
2a	730158K	Adult tablet	400	21.4	18.7	837.0	111.1
2b	730158K	Chewable tablet	150	21.1	7.1	NA	30.4

NA= Not available. No sample collected at 12 hours post dose.

Table 14 Statistical summary of raltegravir PK results obtained from Cohort 2a (≥6 to <12 years) in the final dose cohort.

Cohort	Subject	Actual Dose (mg BID)	Weight (kg)	Dose (mg/kg BID)	C_{12h} (nM)	AUC_{12h} (μM*hr)	C_{max} (μM)
Final Cohort (fasting) 400 mg BID Film-coated tablet	503159A	400	39.1	10.2	86.0	9.6	3.0
	505954F	400	38.0	10.5	266.2	38.0	13.5
	509862G	400	32.7	12.2	133.7	15.1	6.9
	650875J	400	22.7	17.6	96.8	6.3	1.4
	670178A	400	41.0	9.8	594.2	21.0	5.1
	690786K	400	35.9	11.1	697.3	10.6	3.0
	8500413K	400	32.4	12.3	241.9	23.9	8.6
	8500417B	400	32.1	12.5	105.3	5.6	1.6
	N	8	8	8	8	8	8
	Mean	400	34.2	12.0	277.7	16.3	5.4
	SD	0	5.7	2.5	238.3	11.0	4.1
	CV%	0	16.7	20.6	85.8	67.5	76.9
	GM	**400**	**33.8**	**11.8**	**205.1**	**13.4**	**4.1**

Three subjects were excluded from this table. Subjects 650947F and 730158K had AUC_{12h} values of 88.04 and 111.13 μM*hr, respectively, after receiving the final raltegravir dose of 400 mg BID using the film-coated tablets. These two subjects weighed <25 kg and were later re-dosed using chewable tablets at 6 mg/kg. Thus, these subjects should not contribute to the recommended final dose for Cohort 2a.

Subject 470159C originally received raltegravir 300 mg BID and had an AUC_{12h} of 23.2 μM*hr and C_{12h} of 655.4 nM. When the dose for Cohort 2a was changed to 400 mg BID, a repeat PK was performed on this subject at 400 mg BID, with a resulting AUC_{12h} of 1.58 μM*hr and C_{12h} of 11.25 nM. The Sponsor could not explain why the subject had such lower exposure on the second dosing occasion. Because the subject had initially achieved the PK target, it may be reasonable to exclude this subject from the summary table shown above.

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After excluding these three subjects from the PK summary in Cohort 2a, the geometric mean AUC_{12h} (13.4) was slightly lower than the target AUC_{12h} (14 to 25 μM*hr). Nevertheless, individual AUC values from subjects fell within the individual target AUC_{12h} of 5 to 45 μM*hr.

Cohort 2b (≥6 years to <12 years of age) dosed with raltegravir chewable tablets

For ease of dosing, the chewable tablets were available in three strengths: 25, 50, and 100 mg. The 50 mg chewable tablets were phased out after dose finding in Cohorts 2b and 3.

- First mini cohort (n=4):

  Subjects received a dose of raltegravir ~8 mg/kg BID using the chewable tablets under fasting conditions. The dose missed the mean PK target by delivering a GM AUC_{0-12h} of 27.5 μM*hr. Investigators enrolled another mini cohort and lowered the dose to ~6 mg/kg BID.

- Second mini cohort (n=4)

  Subjects received a dose of raltegravir ~6 mg/kg (NTE 300 mg) BID using the chewable tablets under fasting conditions. The dose met the mean PK target by delivering a GM AUC_{0-12h} of 20.1 μM*hr. Investigators enrolled the full cohort to receive the same dose of raltegravir.

- Full cohort (n=10)

  The full-Cohort 2b received raltegravir ~6 mg/kg (NTE 300 mg) BID under fasting conditions using the chewable tablets. The dose met the mean PK target by delivering a GM AUC_{0-12h} of 22.6 μM*hr.

- The final dose recommendation for children ≥6 to <12 years of age weighing <25 kg is raltegravir 6 mg/kg NTE 300 mg BID using the chewable tablets.

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Table 15 Statistical summary of raltegravir PK results obtained from Cohort 2b (≥6 to <12 years) in the final dose cohort.

Cohort	Subject	Actual Dose (mg BID)	Weight (kg)	Dose (mg/kg BID)	C_{12h} (nM)	AUC_{12h} (μM*hr)	C_{max} (μM)
Final Cohort (fasting) 6 mg/kg BID chewable tablet	362602A	200	30.5	6.6	64.7	18.3	8.4
	401162G	300	37.8	7.9	335.3	40.6	21.7
	401171H	250	36.2	6.9	68.4	23.1	11.0
	461086I	200	30.9	6.5	123.5	15.4	4.0
	503862A	150	25.2	6.0	68.0	20.3	9.4
	504261C	300	51.3	5.8	92.5	24.8	15.7
	650976E	200	33.9	5.9	102.8	24.4	6.2
	690743J	150	19.2	7.8	456.8	27.7	23.1
	730073J	300	57.0	5.3	396.5	30.1	12.4
	8500373G	250	41.6	6.0	62.3	12.8	7.8
	N	10	10	10	10	10	10
	Mean	230	36.4	6.5	177.1	23.7	12.0
	SD	58.7	11.4	0.9	155.1	8.0	6.4
	CV%	25.5	31.3	13.2	87.6	33.6	53.5
	GM	**223**	**34.8**	**6.4**	**129.6**	**22.6**	**10.5**

<u>Cohort 3 (≥2 years to <6 years of age) dosed with raltegravir chewable tablets</u>

- First mini cohort (n=4):

  Subjects received a dose of raltegravir ~6 mg/kg (NTE 300 mg) BID using the chewable tablets under fasting conditions. The dose met the mean PK target by delivering a GM $AUC_{0\text{-}12h}$ of 17.2 μM*hr. Investigators enrolled the full-cohort at the same dose of raltegravir.

- Full cohort (n=12):

  Subjects received a dose of raltegravir ~6 mg/kg (NTE 300 mg) BID under fasting conditions using the chewable tablets. The dose met the PK target by delivering a GM $AUC_{0\text{-}12h}$ of 17.9 μM*hr.

- The final dose recommendation for children ≥2 to <6 years of age is raltegravir 6 mg/kg (NTE 300 mg) BID using the chewable tablets.

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Table 16 Statistical summary of raltegravir PK results obtained from Cohort 3 (≥2 to <6 years) in the final dose cohort.

Cohort	Subject	Actual Dose (mg BID)	Weight (kg)	Dose (mg/kg BID)	C_{12h} (nM)	AUC_{12h} (μM*hr)	C_{max} (μM)
Final Cohort (fasting) 6 mg/kg BID chewable tablet	1220166G	150	19	7.9	65.5	35.7	13.2
	362885G	75	12.9	5.8	104.9	15.7	10.0
	*382147E	75	13.6	5.5	6.9	24.3	15.3
	401287D	75	12.8	5.9	116.8	13.3	14.3
	509917K	100	15.0	6.7	40.5	5.4	3.0
	651385G	100	15.2	6.6	160.2	10.4	6.2
	801109F	100	14.9	6.7	96.8	37.0	21.3
	801287L	75	12.0	6.3	185.9	29.8	17.7
	801395B	75	11.8	6.4	86.2	10.7	4.0
	801522K	75	13.1	5.7	62.3	17.2	9.0
	8502057D	100	17.7	5.6	64.8	43.7	22.0
	8502656E	75	12.9	5.8	74.9	12.5	4.8
	N	12	12	12	12	12	12
	Mean	89.6	14.2	6.2	88.8	21.3	11.7
	SD	22.5	2.2	0.7	49.3	12.5	6.6
	CV%	25.1	15.7	10.9	55.5	58.6	56.5
	GM	**87.5**	**14.1**	**6.2**	**71.2**	**18.0**	**9.7**

*C_{8h} was 43.7 ng/mL and C_{12h} was 6283 ng/mL. Dose was administered between 8 and 12 hours of sampling. Extrapolated terminal concentrations to C_{12h}.

The OCP reviewer recommends removing [redacted] (b) (4)

Results of Intensive and Sparse PK data analysis (Stages 1 and 2)

Visual inspection of $AUC_{0\text{-}12h}$ and C_{12h} values obtained by analyzing intensive PK data revealed similar exposure by age and weight at the final proposed doses (see figures below).

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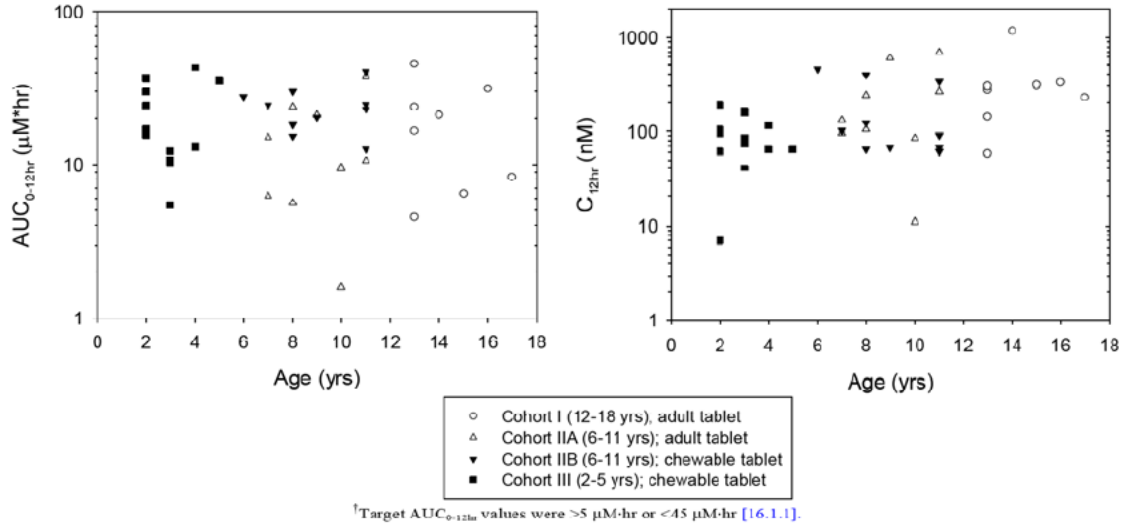
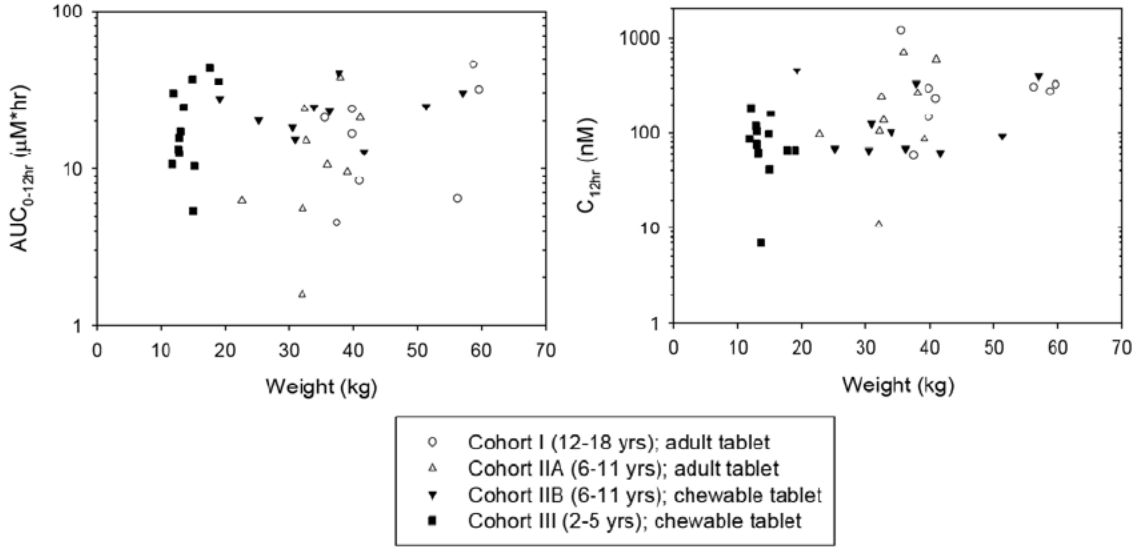
Figure 5 Individual raltegravir $AUC_{0\text{-}12h}$† and C_{12h} as a function of age for pediatric subjects enrolled in Stage 1 and dosed according to final dosing recommendations for each cohort.



†Target $AUC_{0\text{-}12hr}$ values were >5 µM·hr or <45 µM·hr [16.1.1].

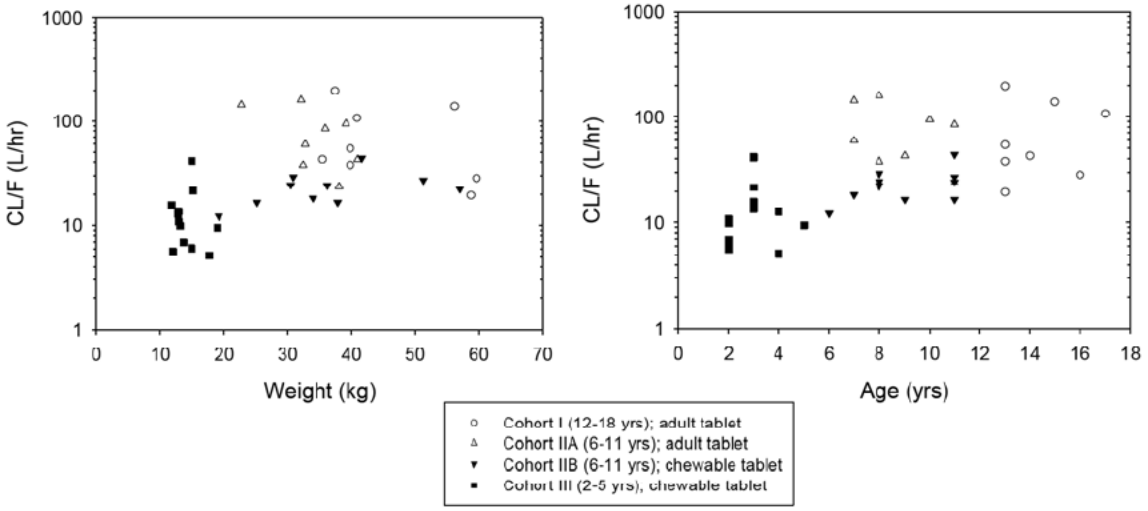
Figure 6 Individual raltegravir $AUC_{0\text{-}12h}$† and C_{12h} as a function of weight for pediatric subjects enrolled in Stage 1 and dosed according to the final dosing recommendations for each cohort



†Target $AUC_{0\text{-}12hr}$ values were >5 µM·hr or <45 µM·hr [16.1.1].
Data Source: [16.4.4]

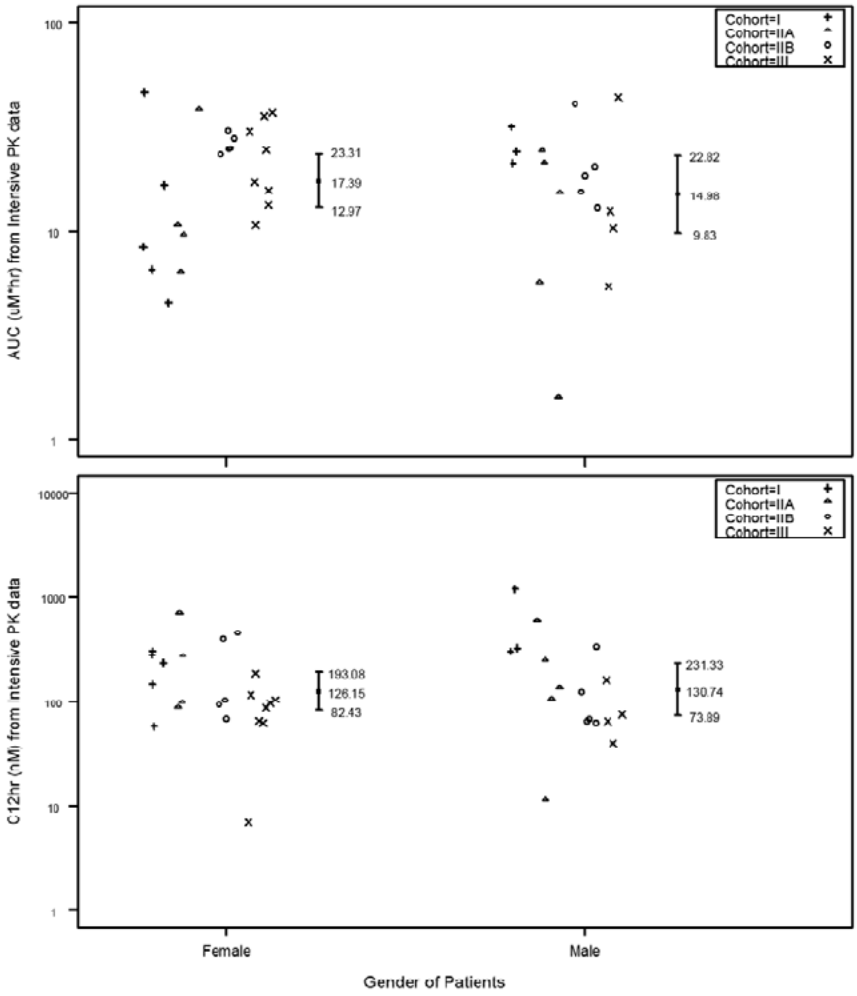
The apparent oral clearance (CL/F) of raltegravir increases as a function of both age and weight before stabilizing in the older (≥6 yrs) and heavier (≥25 kg) children (see figure below).

Figure 7 Individual raltegravir oral clearance (CL/F) as a function of age and weight for pediatric subjects enrolled in Stage 1 and dosed according to the final dosing recommendation for each cohort



Mean raltegravir exposures were similar across males and females receiving the final dose per cohort (see figure below).

Figure 8 Raltegravir intensive PK parameters $AUC_{0\text{-}12h}$ and C_{12h} (GM and 95% CI) for males versus females in Stage 1 (all cohorts pooled)



Analysis of sparse PK collected in Stage 2 and Stage 1 extension of Cohorts 1, 2a, 2b, and 3.

The final doses of raltegravir selected for each cohort maintained steady state GM C_{12h} values >33 nM, the target trough level. For comparison, raltegravir GM C_{12h} values ranged from 11 to 9151 nM in the original NDA in adults receiving 400 mg BID using poloxamer tablets. The following table summarizes results from analysis of sparse PK data collected during Stage 2 in trial P1066 (extension cohorts).

Table 17 Geometric Mean (%CV) values for non-model based raltegravir PK parameters calculated from Sparse Concentration data (Cohorts 1, 2, 2a, 2b, and 3, final dose population).

Cohort	N	C_{all} (nM)	N	GM C_{12hr} (nM)	N	C_{min} (nM)
I	58	354 (112)	53	225 (175)	58	72 (163)
IIA	4	1227 (80)	2	558 (93)	4	262 (51)
IIB	13	355 (82)	12	108 (101)	13	50 (77)
III	20	267 (164)	19	130 (161)	20	57 (170)

For Cohorts 2b and 3, a population PK model was used to calculate raltegravir PK parameters at the final dose using chewable tablets. The table below summarizes calculated steady state geometric mean $AUC_{0\text{-}12h}$, C_{max} and C_{12h} values. Calculated GM $AUC_{0\text{-}12h}$ and C_{12h} values met the predefined PK targets ($AUC_{0\text{-}12h}$ within 14 to 25 μM*hr and C_{12h} >33 nM).

Table 18 GM (%CV) values for model based raltegravir PK parameters calculated from Sparse Concentration Data (Cohorts 2b and 3, final dose using chewable tablets).

Cohort	N	$AUC_{0\text{-}12hr}$ (μM*hr)	C_{max} (μM)	C_{12hr} (nM)
IIB	13	25.3 (23)	10.8 (31)	244 (89)
III	20	19.7 (75)	8.7 (26)	157 (176)

Exposure-response analysis

A logistic regression analysis was conducted using sparse PK data to explore potential associations between raltegravir PK exposures and antiretroviral responses. For all cohorts, three non-model based exposure summary measures were calculated based on observed sparse PK data. This approach was based on prior experience in adults with adult tablets, where a population PK model could not be developed due to variability in absorption. The analysis included parameters such as C_{all}, GM C_{12h}, and proportion of subjects achieving ≥1 log drop or HIV RNA <400 copies/mL and HIV RNA <50 copies/mL. When the analysis included data from all cohorts, there was a statistically significant ($p<0.05$) association between C_{all} and GM C_{12h} with all efficacy parameters evaluated (See table below). When separating data into formulations, the PK/PD association remained statistically significant for Cohorts 1 and 2a (adult tablets), but not for Cohorts 2b and 3 (chewable tablets).

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Table 19 Estimated odds ratio with 95% CI and p-value for PK parameters as predictors for antiretroviral responses (all cohorts, final dose population).

	n[§]	N[§]	Odds Ratio (95% CI)[†]	p-Value[†]
Patients in all four Cohorts (I, IIA, IIB & III)				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	63	85	3.094 (1.110, 8.629)	0.031
Geo Mean of All Observed Conc. (nM) from Sparse PK data	68	94	2.781 (1.145, 6.750)	0.024
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	47	85	4.340 (1.674, 11.256)	0.003
Geo Mean of All Observed Conc. (nM) from Sparse PK data	51	94	2.934 (1.286, 6.693)	0.011
Patients in Cohorts I & IIA only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	41	54	8.668 (1.729, 43.455)	0.009
Geo Mean of All Observed Conc. (nM) from Sparse PK data	44	61	3.896 (1.284, 11.817)	0.016
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	32	54	16.106 (2.998, 86.514)	0.001
Geo Mean of All Observed Conc. (nM) from Sparse PK data	34	61	4.365 (1.457, 13.081)	0.008
Patients in Cohorts IIB & III only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	22	31	0.326 (0.046, 2.288)	0.260
Geo Mean of All Observed Conc. (nM) from Sparse PK data	24	33	1.642 (0.291, 9.248)	0.574
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	15	31	0.763 (0.170, 3.421)	0.724
Geo Mean of All Observed Conc. (nM) from Sparse PK data	17	33	1.580 (0.395, 6.315)	0.517

[†] Logistic regression with PK parameters (in $\log_{10}$ scale) and following covariates: baseline HIV RNA ($\log_{10}$ copies/mL).
[§] N: number of patients with both PK and efficacy data. n: number of patients (out of N) with events.

The logistic regression analysis was re-examined to evaluate the effect of medication non-compliance on probability of achieving antiretroviral response. Initial data analysis revealed that several subjects had multiple raltegravir concentration values that were below the assay limit of quantification (BLOQ). The Sponsor postulated that subjects with multiple PK samples BLOQ were likely to be non-compliant with raltegravir therapy and to have poor antiretroviral response. In further support of this hypothesis, subjects with multiple BLOQ values were also reported to have taken fewer pills than expected on at least 1 visit. When the analysis excluded subjects with ≥2 PK samples BLOQ, a statistical significant relationship remained only between GM C_{12h} and HIV RNA <50 copies/mL (See table below) in subjects receiving the adult tablet. The Sponsor could not explain the meaning of this PK/PD relationship, and warns that the relationship should be interpreted with caution due to the relatively small number of subjects in Cohorts 1 and 2a, the small number of samples that went into the GM C_{12h} value (median of 2 samples per subject), and large inter- and intra-subject PK variability of raltegravir.

Reference ID: 3054777

Table 20 Population PK parameters as a predictor for antiretroviral responses (all cohorts excluding subjects with ≥2 BLOQ PK values, final dose population).

	n[§]	N[§]	Odds Ratio (95% CI)[†]	p-Value[†]
Patients in all four Cohorts (I, IIA, IIB & III)				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	60	73	1.337 (0.389, 4.591)	0.645
Geo Mean of All Observed Conc. (nM) from Sparse PK data	64	81	0.674 (0.173, 2.617)	0.568
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	45	73	3.188 (1.109, 9.167)	0.031
Geo Mean of All Observed Conc. (nM) from Sparse PK data	48	81	2.038 (0.677, 6.140)	0.206
Patients in Cohorts I & IIA only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	40	46	3.776 (0.530, 26.909)	0.185
Geo Mean of All Observed Conc. (nM) from Sparse PK data	42	52	1.118 (0.207, 6.041)	0.897
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	31	46	12.756 (1.967, 82.735)	0.008
Geo Mean of All Observed Conc. (nM) from Sparse PK data	32	52	4.075 (0.929, 17.872)	0.062
Patients in Cohorts IIB & III only				
>=1 log10 Drop from Baseline or HIV RNA < 400 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	20	27	0.199 (0.020, 2.018)	0.172
Geo Mean of All Observed Conc. (nM) from Sparse PK data	22	29	0.317 (0.026, 3.884)	0.369
HIV RNA <50 copies/mL at week 24				
Geo Mean of C12hr (nM) from Sparse PK data	14	27	0.509 (0.091, 2.835)	0.441
Geo Mean of All Observed Conc. (nM) from Sparse PK data	16	29	0.652 (0.096, 4.434)	0.662

[†] Logistic regression with PK parameters (in $\log_{10}$ scale) and following covariates: baseline HIV RNA ($\log_{10}$ copies/mL).

[§] N: number of patients with both PK and efficacy data. n: number of patients (out of N) with events.

NOTE: Patients who have 2 or more BLOQ concentration and/or dose changed during the study are excluded.

In the original NDA, the exposure-response relationship of raltegravir C_{12h} and virologic success was shallow in adults. The PK/PD analysis included data from two large, double blind, placebo controlled trials (Protocols 018 and 019) in HIV-infected, treatment-experienced adult subjects with documented resistance to at least one ARV. The analysis included 483 subjects (225 raltegravir + OBT treated and 228 placebo + OBT treated). In the raltegravir arms, subjects received raltegravir 400 mg BID using poloxamer tablets in combination with OBT for 16 weeks (data cut off at that time). The PK parameters of interest were GM C_{12h} and the minimum observed C_{12h}, both parameters determined from all samples taken between 11 and 13 hours post dose in a given individual. The PD parameters of interest were the proportion (%) of subjects achieving HIV RNA <50 copies/mL or <400 copies/mL at week 16.

Within the raltegravir concentration range studied, virologic success rates were similar (77%) for subjects with lower C_{12h} values (median C_{12h}= 76 nM) compared to those with higher C_{12h} values (median C_{12h}= 1085 nM), as shown below.

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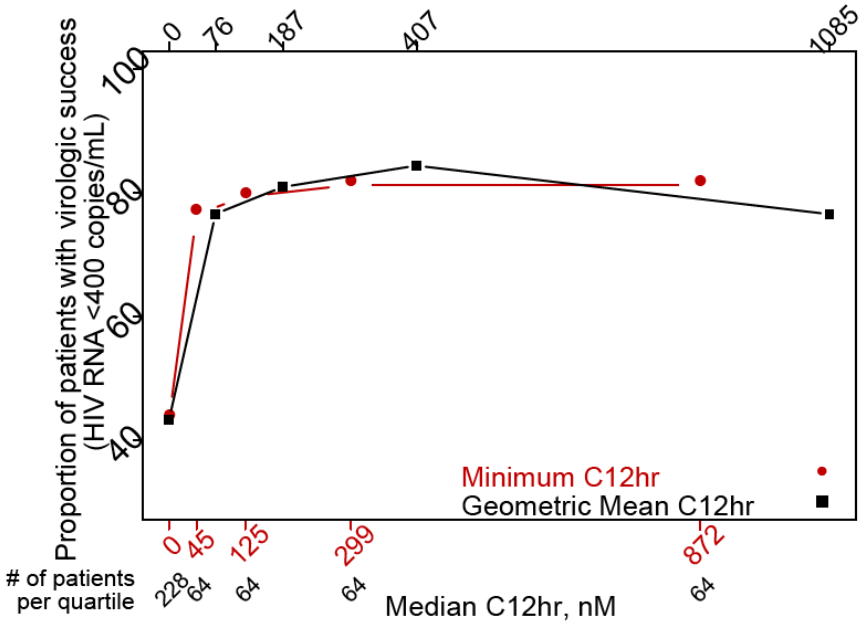
Figure 9 C_{12h}-virologic success relationship. The C_{12h}=0 represents placebo-treated patients; raltegravir-treated patients were divided into four quartiles.



The initial OCP reviewer noted that this PK/PD relationship needed careful interpretation in the presence of high within subject variability. The lack of relationship could have been due to high within subject variability leading to uncertain measure of individual exposure or due to high potency (as demonstrated by maximum *in vitro* IC_{95} ~ 50nM in 50% human serum) of raltegravir such that the exposures were in the asymptotic region of the C_{12h} - virologic success relationship. Also of note, BLOQ values were treated as missing in the adult analysis, while in the current analysis in children, BLOQ values were assigned a value of 11 nM (1/2 x LLOQ).

Efficacy results up to 24 weeks of treatment with the final dose of raltegravir

Efficacy data are currently available from subjects in all cohorts who received the final dose of raltegravir in combination with other antiretrovirals for up to 24 weeks. The proportion of subjects with HIV RNA <50 copies/mL in Cohorts 1, 2a, 2b, and 3 was 55.2%, 50%, 53.8%, and 50%, respectively. The overall proportion of subjects with HIV RNA <50 copies/mL across all cohorts was 53.7%. In contrast, the proportion of adult subjects (n=466) achieving HCV RNA <50 copies/mL was 55% after receiving raltegravir 400 mg BID doses for 96 weeks.

Decreases in viral loads were accompanied with increases in CD4 cell counts from baseline across cohorts, except in Cohort 2a. Mean CD4 cell counts in Cohort 2a decreased by 36% from baseline. The explanation for this observation

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could be related to low subject numbers (n=4) enrolled in this cohort at the final proposed dose. The table below summarizes efficacy results per cohort in subjects receiving the final dose for 24 weeks.

Table 21 Efficacy analysis by cohort, Final dose population, Week 24 results, 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	42/58	72.4 (59.1, 83.3)	2/4	50 (6.8, 93.2)	10/13	76.9 (46.2, 95)	14/20	70 (45.7, 88.1)	68/95	71.6 (61.4, 80.4)
Proportion of patients with HIV RNA <50 copies/mL	32/58	55.2 (41.5, 68.3)	2/4	50 (6.8, 93.2)	7/13	53.8 (25.1, 80.8)	10/20	50 (27.2, 72.8)	51/95	53.7 (43.2, 64)
Proportion of patients with HIV RNA <400 copies/mL	40/58	69 (55.5, 80.5)	2/4	50 (6.8, 93.2)	9/13	69.2 (38.6, 90.9)	12/20	60 (36.1, 80.9)	63/95	66.3 (55.9, 75.7)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in CD4 cell count (cells/mm3)	114.4	(73.7, 155.1)	-35.8	(-348.8, 277.3)	143.4	(-12.9, 299.6)	147.2	(-2.7, 297.1)	119.0	(74.9, 163.1)
Change from baseline in CD4 percent	4.1	(2.8, 5.3)	2.2	(-7.2, 11.5)	0.8	(-3.6, 5.2)	5.3	(2.9, 7.7)	3.8	(2.7, 4.9)

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.
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.

Efficacy results up to 48 weeks of treatment with the final dose of raltegravir

Efficacy data up to 48 weeks are currently available for Cohorts 1, 2a, and 2b only. Similar to Week 24 efficacy data, the proportion of subjects who had HIV RNA <50 copies/mL in Cohorts 1, 2a, and 2b was 57.1%, 50%, and 54.5%, respectively. Efficacy data are pending for Cohort 3. The mean change from baseline in CD4 cell counts are also comparable to values observed at Week 24. The table below summarizes efficacy results for Cohorts receiving raltegravir at the final dose for up to 48 weeks.

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Table 22 Efficacy analysis by cohort, Final dose population, Week 48 results, Observed failure approach.

Parameter	Cohort I (N=59)		Cohort IIA (N=4)		Cohort IIB (N=13)		Total (N=76)	
	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)	55/71	77.5 (66, 86.5)
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)	40/71	56.3 (44, 68.1)
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)	51/71	71.8 (59.9, 81.9)
	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)	155.1	(107.9, 202.2)
Change from baseline in CD4 percent	5.2	(3.9, 6.6)	6.0	(-2.6, 14.6)	1.6	(-2.7, 5.9)	4.7	(3.4, 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.
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.

Safety

Table 23 Summary of clinical adverse events by cohort; final dose population, Weeks 0-24.

	Cohort I (N=59)	Cohort IIA (N=4)	Cohort IIB (N=13)	Cohort III (N=20)	Total (N=96)
	n (%)	n (%)	n (%)	n (%)	n (%)
With one or more clinical adverse events	50 (84.7)	3 (75)	10 (76.9)	14 (70)	77 (80.2)
With no clinical adverse event	9 (15.3)	1 (25)	3 (23.1)	6 (30)	19 (19.8)
With one or more serious clinical adverse events	9 (15.3)	0 (0)	2 (15.4)	2 (10)	13 (13.5)
With one or more serious drug related† clinical adverse events	0 (0)	0 (0)	0 (0)	1 (5)	1 (1)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
With one or more Grade 3 or greater clinical adverse events	8 (13.6)	0 (0)	2 (15.4)	3 (15)	13 (13.5)
With one or more Grade 3 or greater drug related† clinical adverse events	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (1)

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.

Summary of Results

Final Dose Population

- The final recommended doses of raltegravir for children and adolescents using poloxamer and chewable tablets delivered a range of exposures similar to those observed in adults receiving raltegravir 400 mg BID using poloxamer tablets.

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- Individual and composite mean virologic success rates at week 24 observed across all pediatric cohorts were similar to virologic success rates observed in adults at week 96.

- A statistically significant exposure-response relationship between raltegravir GM C_{12h} values and proportion of subjects achieving HIV RNA <50 copies/mL was observed in Cohorts 1 and 2a receiving poloxamer tablets. The exposure-response relationship is not fully understood, but the Applicant believes it may be due to medication non-compliance. The Applicant states the results of the observed PK/PD relationship should be interpreted with caution due to the small number of subjects, large inter- and intra-subject variability in raltegravir PK, and the small number of samples used in calculating GM C_{12h} for each subject (median= 2).

  Nevertheless, the exposure-response relationship will not affect the overall conclusion that the final pediatric doses of raltegravir are adequate based on intensive PK results and because virologic success rates in pediatrics were similar to those observed in adults.

- The frequency and severity of raltegravir-related adverse events in pediatrics were comparable to those observed in adults. Gastrointestinal disorders were more common in pediatrics (46.9%) compared to adults (2%).

- Overall, the final doses of raltegravir in pediatrics deliver comparable PK, safety, and efficacy relative to adults.

- The Office of Scientific Investigations (OSI) inspected the laboratory responsible for the bioanalysis of all plasma samples collected in this trial. Following an onsite inspection of the (b) (4) OSI reported the PK data were acceptable for FDA review. Thus, all PK data presented in this trial report are considered reliable.

3.1.2 Trial P068

A single-dose trial comparing the PK of three raltegravir (MK-0518) formulations and evaluate the effect of food on the pharmacokinetics of one formulation.

Trial Period

Trial initiation: June 21, 2008
Trial completion: Undisclosed

Reference ID: 3054777

Trial site

Covance Clinical Research Unit, Inc., in Dallas, Texas, US.

Trial Population

Twelve healthy subjects, including adult males and females.

Trial Rationale

Raltegravir is indicated for the treatment of HIV-1 infection in adults. The current formulation of raltegravir is a poloxamer tablet suitable for adults. Because HIV infection is not limited to adults, Merck developed two raltegravir formulations that are appropriate for treating children: an ethylcellulose chewable tablet and a granular formulation for suspension. This trial compared the PK of raltegravir administered as poloxamer versus chewable tablets. This review will not discuss results for the granular formulation because the sNDA does not seek approval for this formulation.

Trial Objectives

Primary:

- Evaluate and compare raltegravir plasma PK profiles following single-dose administration of poloxamer formulation and ethylcellulose (EC) formulation in healthy adult subjects.

Secondary:

- Compare raltegravir plasma PK profiles following single-dose administration of raltegravir as EC formulation in the fasted state and following a high fat meal in healthy adult subjects.

Trial Design

This Phase 1 trial had an open-label, four-period, randomized, crossover design. Subjects received a single 400 mg dose of raltegravir in four periods. A 4-day washout period was observed before beginning a new treatment period. Treatments A and B were administered in the fasted state, and treatment D was administered after ingesting a high fat meal. Treatment A was dosed using the commercially available poloxamer tablet. The following table displays the trial design and raltegravir treatments.

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Table 24 Sample allocation schedule

	Treatment Periods			
n	Period 1	Period 2	Period 3	Period 4
3	A	B	C	D
3	B	C	D	A
3	C	D	A	B
3	D	A	B	C

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)

Note: This review will not discuss results from Treatment C, oral granule formulation. The 400 mg dose of raltegravir was delivered using 4 X 100 mg chewable tablets and 1 X 400 mg poloxamer tablet.

Key Inclusion/Exclusion Criteria

Inclusion

All subjects were required to meet the following criteria prior to trial enrollment:

- Men and women 18 to 55 years of age.
- Body mass index (BMI) ≤ 35 kg/m^2.
- Normal blood pressure, pulse rate, 12-lead ECGs, and hematology tests.
- Normal renal function (CrCl >70 mL/min calculated using Cockcroft-Gault equation).
- Women must have had a negative pregnancy test and agree to use at least two acceptable methods of contraception during the trial, including intrauterine devices (+/- hormone release), diaphragm, spermicide, cervical caps, contraceptive sponges, condoms, or abstinence from sexual intercourse.

Exclusion

The trial excluded subjects who met one or more of the following criteria:

- Positive HIV infection.
- Women who were pregnant or breastfeeding.
- Severe medical condition including stroke, cardiovascular disease, chronic seizures, hepatic or renal abnormalities.
- History of substance abuse, excessive intake of alcohol, caffeinated drinks, or tobacco smoking.

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- Ingestion of prescription and non-prescription drugs (except acetaminophen), or herbal remedies before starting and during the trial. Additional dietary restrictions included consumption of grapefruit products at least 2 weeks before trial start.
- Oral contraceptives were not allowed as a method of birth control in this trial.

Rationale for Dose Selection

The recommended dose of raltegravir for HIV-1 treatment in adults is 400 mg BID. Raltegravir exhibits linear PK, with single doses predicting multiple dose exposures. For this reason, a single dose 400 mg raltegravir was appropriate for comparing the PK of raltegravir delivered as two different formulations. Food increases the PK variability of raltegravir. Therefore, the poloxamer tablets and chewable tablets were administered in the fasting state in treatments A and B, except for treatment D. In treatment D, chewable tablets were administered with a high fat meal.

Investigational Product

This trial tested two formulations of raltegravir. The table below lists the formulations.

Table 25 Identity of raltegravir formulations tested in trial P068

Formulation	Dosage Form	Dose	Formulation number	Assay potency
Raltegravir/Isentress™	Commercially available tablet	1 X 400 mg	WL00022441	100.6%
Raltegravir pediatric ethylcellulose chewable (EC)	Newly developed tablet	4 X 100 mg	WL00025332	98.6%

Drug Administration

On day 1 of treatments A and B, subjects received a single dose of raltegravir 400 mg under fasting conditions with water (240 mL). Additional food and water intake was regulated. Water intake was prohibited within 1 hour before and after raltegravir dosing. Food intake was prohibited 4 hours post dose.

On day 1 of treatment D, subjects fasted overnight (~8 hours) before raltegravir dosing. On the morning of dosing, subjects were instructed to consume an entire high fat meal within 25 minutes prior to receiving raltegravir. Subjects ingested a single dose of raltegravir 400 mg chewable tablets with water (240 mL). Additional food and water intake was regulated, as described above.

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The high fat meal contained 55.6 g of fat, 55 g of carbohydrates, and 31.1 g of protein.

Table 26 Ingredients of the high-fat meal (827 kcal, 57% fat content)

2 fried or scrambled eggs
2 strips bacon
2 slices toast with 2 pats of butter
4 oz (113 g) hash browns (fried potato)
240 mL whole milk

Pharmacokinetic Sampling

Raltegravir plasma samples were collected on day 1 of treatments A, B, and D immediately prior to dosing (0) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, and 72 hours post dose.

Pharmacokinetic Analyses

This trial evaluated the PK of raltegravir following a single 400 mg dose administered as poloxamer and chewable tablets under fasting conditions. The primary PK variable was C_{12h}, but $AUC_{0\text{-}inf}$, C_{max}, T_{max}, and apparent $t_{1/2}$ were also evaluated. The secondary variables of interest were raltegravir $AUC_{0\text{-}inf}$ and C_{12h} following a single dose of 400 mg chewable tablet administered in fasted or fed (high fat meal) conditions.

Statistical Analyses

This trial used a linear mixed-effect model to evaluate the effect of formulation on single dose plasma PK of raltegravir. The model assigned fixed effects terms for treatment and period, and a random effect term to subject. The model calculated two-sided 90% confidence intervals (90% CI) for the geometric mean ratio (GMR) of raltegravir C_{12h}, $AUC_{0\text{-}inf}$, and C_{max} for poloxamer tablet formulation versus chewable tablet formulation. A similar linear-mixed effect model was used to evaluate the GMR of raltegravir $AUC_{0\text{-}inf}$ and C_{max} when chewable tablets were administered under fed versus fasting conditions.

Bioanalytical Methods

The method and bioanalysis of raltegravir is acceptable. All plasma samples for raltegravir were analyzed by [redacted] (b) (4),

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(b) (4) technicians analyzed samples using a validated LC-MS/MS method (No. SAP.761) in compliance with Merck standard operating procedures. Bioanalytical performance was documented in (b) (4) study report 0094-08280.

Plasma samples of raltegravir in K_2EDTA were properly stored prior to bioanalysis. Raltegravir is stable in plasma for up to 23 months when stored at -20ºC. (b) (4) stored the plasma samples at -20ºC, and analyzed them within 24 days of collection.

The following table summarizes the performance of the bioanalytical method. The upper and lower limits of quantification were 2.0 and 1000 ng/mL, respectively.

Table 27 Summary of method performance

Parameter	Precision (% CV)		Accuracy (% Bias)	
	From	To	From	To
Intra Run (N=6)	2.64	8.10	-3.96	10.6
Inter Run (N=18)	3.27	6.17	-2.43	8.99

Results

Subject demographics

The following table summarizes demographics of trial subjects.

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Table 28 Demographic characteristics

AN	Gender	Race	Ethnicity	Age	Height	Weight	BMI
0001	Female	White	Hispanic or Latino	45	161.3	54	20.76
0002	Female	White	Hispanic or Latino	28	155.5	59.2	24.48
0003	Male	White	Not Hispanic or Latino	52	192	89.4	24.25
0004	Male	White	Not Hispanic or Latino	37	187.6	81.5	23.16
0005	Female	White	Hispanic or Latino	39	156.4	73.1	29.88
0006	Male	White	Hispanic or Latino	47	165.8	81.6	29.68
0007	Male	Black	Not Hispanic or Latino	39	178.6	91	28.53
0008	Male	White	Not Hispanic or Latino	50	173	78.3	26.16
0009	Male	White	Not Hispanic or Latino	46	185.7	95.3	27.64
0010	Male	White	Hispanic or Latino	43	166	78.5	28.49
0011	Male	Black	Not Hispanic or Latino	26	170.3	91.2	31.45
0012	Male	White	Hispanic or Latino	29	166.2	62.8	22.74
Study Summary							
N:				12	12	12	12
Range:				26 to 52	155.5 to 192	54 to 95.3	20.8 to 31.4
Mean:				40	171.5	78.0	26.4
Female N:				3	3	3	3
Female Range:				28 to 45	155.5 to 161.3	54 to 73.1	20.8 to 29.9
Female Mean:				37	157.7	62.1	25.1
Male N:				9	9	9	9
Male Range:				26 to 52	165.8 to 192	62.8 to 95.3	22.7 to 31.4
Male Mean:				41	176.1	83.3	26.9

AN=Allocation number.

Pharmacokinetics

Plasma exposures of raltegravir where higher when administered as ethylcellulose chewable tablets compared to commercial poloxamer tablet formulation under fasting conditions. Mean raltegravir $AUC_{0\text{-}inf}$ and C_{max} values were 78% and 222% higher with the chewable tablets compared to poloxamer tablets following a single 400 mg dose. On the other hand, raltegravir C_{12h} values were similar for both formulations (GMR 90% CI: 0.90 [0.7, 1.18]). The table below summarizes statistical results for the comparison between treatments A and B.

Table 29 Summary Statistics of raltegravir plasma PK following single dose administration of poloxamer tablets and ethylcellulose chewable tablets under fasting conditions in healthy adult subjects.

PK parameter (units)	N	Treatment A GM[1]	Treatment B GM[1]	Comparison	GMR (90% CI)
C_{12h} (nM)[2]	12	149	134	B/A	0.90 (0.70, 1.18)
$AUC_{0\text{-}inf}$ (μM*hr)[2]	12	19.2	34.2	B/A	1.78 (1.47, 2.15)
C_{max} (μM)[2]	12	5.0	16.1	B/A	3.22 (2.37, 4.38)
T_{max} (hr)[3]	12	4.0	0.5		
$t_{1/2l}$ (hr)[4]		1.5 (0.3)	1.7 (0.2)		
$t_{1/2T}$ (hr)[4]	12	9.0 (5.9)	9.3 (5.1)		

[1] Treatment A= Raltegravir 400 mg poloxamer tablet, fasting
Treatment B= Raltegravir 400 mg chewable tablet, fasting
[2] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
[3] Median values presented for T_{max}.
[4] 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, and D are 11, 12, and 10, respectively.

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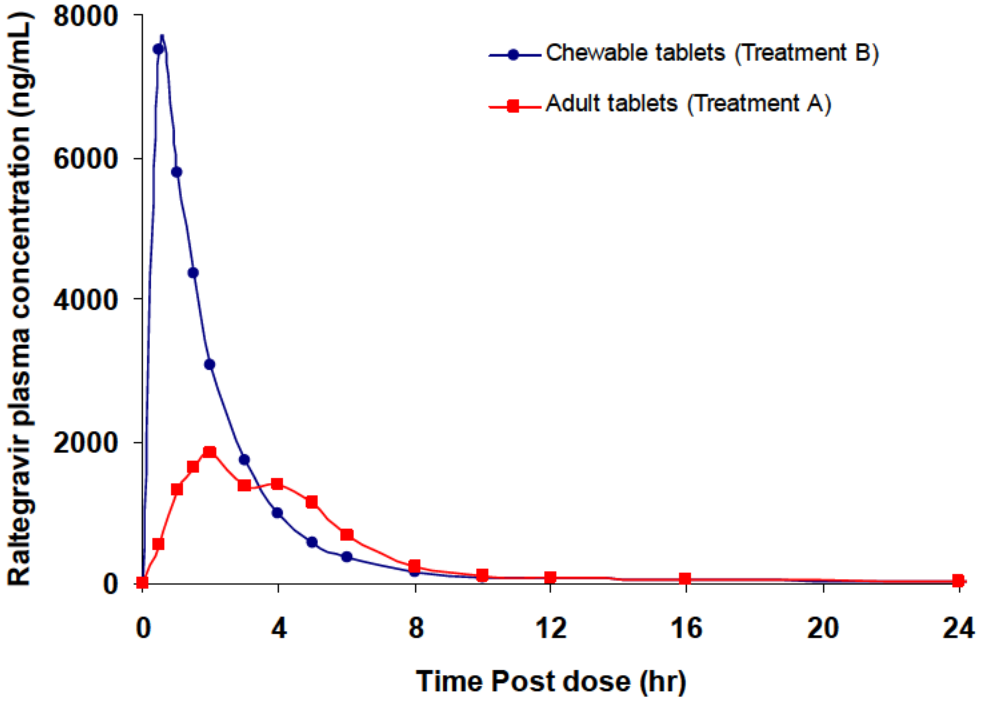
Mean plasma concentration-time profiles of raltegravir following a 400 mg single dose are displayed below. The chewable tablets delivered considerably higher (2.2-fold) mean C_{max} values relative to poloxamer tablets under fasting conditions. The median T_{max} of raltegravir occurred earlier (0.5 h) with chewable tablets relative to poloxamer tablets (~4 h).

Figure 10 Mean plasma concentration-time profile of single dose 400 mg raltegravir administered under fasting conditions using poloxamer tablets (A) versus chewable tablets (B) (n=12).



Food slowed the rate of raltegravir absorption, but it did not affect the extent of absorption compared to fasting conditions when using chewable tablets. Administration with a high fat meal decreased mean C_{max} values by 62%, delayed median T_{max} by 0.5 hours, but did not affect mean $AUC_{0\text{-}inf}$ values (GMR 90% CI= 0.94 [0.78, 1.14]) compared to fasting conditions. Food increased mean C_{12h} values by 188% relative to fasting. The table below summarizes statistical results for the comparison between treatments B and D.

Table 30 Summary Statistics of raltegravir plasma PK following single dose administration of ethylcellulose chewable tablets under fed (D) and fasting (B) conditions in healthy adult subjects.

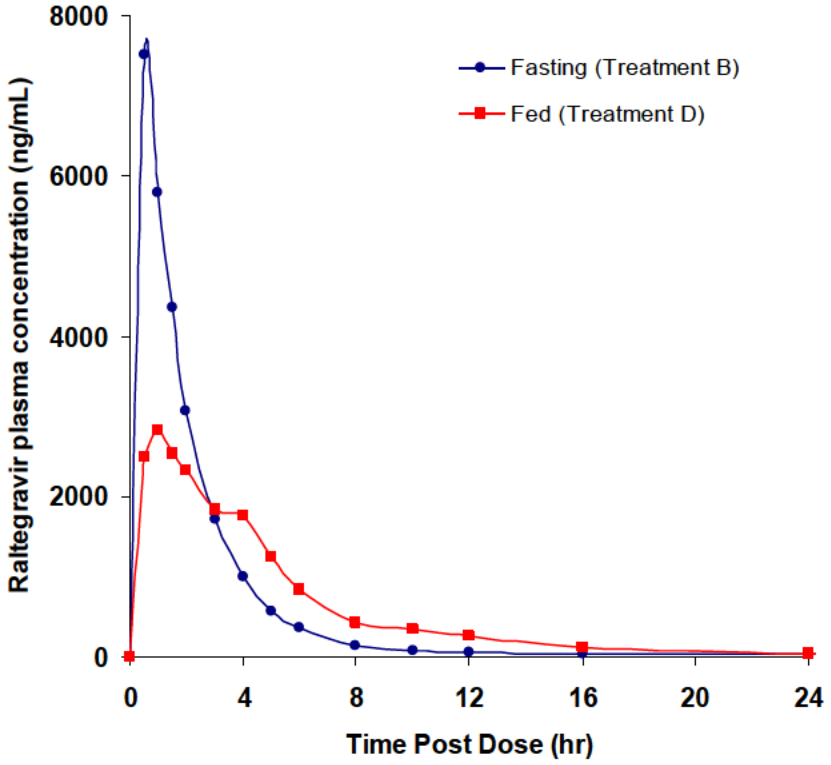
PK parameter (units)	N	Treatment B GM[1]	Treatment D GM[1]	Comparison	GMR (90% CI)
C_{12h} (nM)[2]	12	134	387	D/B	2.88 (2.21, 3.75)
$AUC_{0\text{-}inf}$ (μM*hr)[2]	12	34.2	32.3	D/B	0.94 (0.78, 1.14)
C_{max} (μM)[2]	12	16.1	6.14	D/B	0.38 (0.28, 0.52)
T_{max} (hr)[3]	12	0.5	1.0		

[1] Treatment B= Raltegravir 400 mg chewable tablet, fasting
Treatment D= Raltegravir 400 mg chewable tablet, fed (high fat meal)
[2] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
[3] Median values presented for T_{max}.

Mean plasma concentration-time profiles of raltegravir administered under fed or fasting conditions using the chewable tablets are displayed below. A high fat meal decreased the mean C_{max} of raltegravir by 62%, and delayed median T_{max} by 0.5 relative to fasting conditions. However, mean raltegravir exposures ($AUC_{0\text{-}inf}$) were similar with both formulations.

Reference ID: 3054777

Figure 11 Mean plasma concentration-time profile of single dose 400 mg raltegravir administered under fasting and fed (high fat meal) conditions using the chewable tablets (n=12).



Summary of Results

Comparison between poloxamer and chewable tablets under fasting conditions:

- The geometric mean ratios of raltegravir $AUC_{0\text{-}inf}$ and C_{max} increased by 78% and 222% respectively when raltegravir was administered as chewable tablets compared to poloxamer tablets.
- The geometric mean ratio of raltegravir C_{12h} was similar for both formulations.

Comparison between fed and fasted conditions using chewable tablets:

- The geometric mean ratio of raltegravir C_{12h} increased by 188% when raltegravir was administered immediately after ingesting a high fat meal relative to fasting conditions.

- The geometric mean ratio of raltegravir C_{max} decreased by 62% when raltegravir was administered immediately after ingesting a high fat meal relative to fasting conditions.

- The high fat meal delayed raltegravir median T_{max} by 0.5 hours relative to fasting conditions.

- The geometric mean ratio of raltegravir $AUC_{0\text{-}inf}$ was unchanged when raltegravir was administered immediately after ingesting a high fat meal relative to fasting conditions.

Conclusion

The ethylcellulose chewable tablets deliver higher raltegravir exposures ($AUC_{0\text{-}inf}$ and C_{max}) relative to commercially available poloxamer tablets under fasting conditions. Thus, chewable and poloxamer tablets are not bioequivalent and should not be used interchangeably at the same dose in a clinical setting.

When using chewable tablets, food delayed the rate of raltegravir absorption, but it did not affect the AUC of raltegravir relative to fasting conditions. The trough levels of raltegravir were higher when chewable tablets were administered with a high fat meal relative to fasting conditions. Food decreased the C_{max} of raltegravir by 62% compared to fasting conditions. A similar food effect on C_{max} (↓ 34%) was previously observed with the poloxamer tablets in the original NDA for raltegravir.

Because a high fat meal did not affect the AUC of raltegravir, the chewable tablets may be administered without regard to food. This recommendation is consistent with food effect information in the current label for Isentress™.

Reference ID: 3054777

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/s/

RUBEN C AYALA
12/06/2011

SARAH M ROBERTSON
12/06/2011

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	NDA203045/ NDA022145 (Supplement 22, SDN 230)	**Brand Name**	Isentress Chewable Tablets
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	Raltegravir
Medical Division	DAVP	**Drug Class**	HIV-1 integrase inhibitor
OCP Reviewer	Ruben Ayala	**Indication(s)**	HIV-1 treatment
OCP Team Leader	Sarah Robertson	**Dosage Form**	25 mg and 100 mg pediatric chewable tablets
Pharmacometrics Reviewer	Jeffry Florian	**Dosing Regimen**	12 yrs of age and older: 1 X 400 mg tablet BID 6-11 yrs of age (2 dosing options): a) 1 X 400 mg tablet BID (if at least 25 kg in weight) or b) Chewable tablet: weight based to maximum dose 300 mg BID 2-5 yrs of age: Chewable tablets: weight based to maximum dose 300 mg BID
Date of Submission	06/30/2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	12/06/2011	**Sponsor**	Merck, Inc.
PDUFA Due Date	12/30/2011	**Priority Classification**	Priority review

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.	**X**			
Tabular Listing of All Human Studies	**X**	**2**		
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**2**		
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				

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

single dose:				
multiple dose:	**X**	**1**		
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:				
pediatrics:	**X**	**1**		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:		**1**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**1**		
Data sparse:	**X**	**1**		
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	**X**	**1**		
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	**2**			

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	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

	satisfying the CFR requirements?				
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		Reports are difficult to read. Will ask Sponsor to re-submit reports using a different font.
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			
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?		X		For this NDA, the Sponsor submitted data collected from subjects 2 to <19 yrs of age. (b)(4) [redacted]

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

					(b) (4)
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.

At this moment, we have not identified major potential review issues in the submission. We will request the Sponsor to re-submit 3 data reports using a different, more readable font.

Ruben Ayala, Pharm.D. 07/29/2011

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

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/s/

RUBEN C AYALA
07/29/2011

SARAH M ROBERTSON
07/29/2011