CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205786Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 4, 2013
From	Yodit Belew, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/NDA # Supplement #	NDA 205786 sNDA 203045(S-09) sNDA 22145 (S-31)
Applicant	Merck
Date of Submission	June 25, 2013
PDUFA Goal Date	December 27, 2013
Proprietary Name / Established (USAN) names	Isentress(raltegravir)
Dosage forms / Strength	New proposed dosage formulation: Oral (b) (4) Suspension Approved dosage forms: film-coated tablets/400 mg; chewable tablets/ 25mg, 100mg
Proposed Indication(s)	Treatment of HIV infection in children 4 weeks (b) (4) (b) (4)
Recommended:	Approval

1. Introduction

This cross discipline team leader review presents the main findings for raltegravir Oral (b) (4) Suspension (b) (4). This review highlights the pharmacokinetics, safety and efficacy (antiviral activity) and overall risk/benefit assessment to support my recommendation for approval for this NDA. The intent of the current application is to expand the intended population to 4 weeks of age and weighing at least 3 kg.

2. Background

Raltegravir, an inhibitor of the catalytic activity of HIV-1 integrase, was originally approved in October, 2007. Raltegravir (film-coated tablets, 400mg strength) is approved for treatment of HIV infection in treatment naïve and experienced adults. Both the film coated tablets and the chewable tablets were evaluated and approved in December 2011 for treatment of HIV infection in pediatric patients 2 years of age and older. The recommended dose of raltegravir in treatment naïve and experienced adult patients is 400 mg of the film-coated tablets, taken twice daily. The recommended dose of raltegravir in pediatric patients is as follows:

<u>12 years of age and older</u>

- One 400 mg tablet BID.

<u>6 through 11 years of age</u>

- One 400 mg tablet BID (if body weight ≥25 kg), OR

- Weight-based dosing not to exceed 300 mg BID using chewable tablets (see table below).

2 through 5 years of age

- Weight-based dosing not to exceed 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)			(b) (4)
(b) (4) to <28	(b) (4) to <62	150 mg twice daily	1.5 X 100 mg*
28 to <40	62 to <88	200 mg twice daily	2 X 100 mg
at least 40	at least 88	300 mg twice daily	3 X 100 mg

*The 100 mg chewable tablet can be divided into equal halves.

A new NDA application and two sNDAs were submitted in support of raltegravir dosing in children 4 weeks (b) (4): NDA 205786, sNDA 22145 and 203045. A new NDA (205786) was created because a new form- oral granules for suspension (GFS) was formulated. Data from children 4 weeks to less than 2 years of age who were administered the GFS was submitted to this NDA while long-term safety data for children 2 to 18 years of age who received the film-coated tablet or the chewable tablets were submitted to the sNDAs. In addition, since all formulations share the same USPI, all information is also cross-referenced to each NDA.

The proposed dosing regimen for pediatric patients 4 weeks (b) (4) is as follows:

Body Weight (kg)	Dose	Volume of Suspension to be Administered
3.0 to less than (b) (4)	20 mg twice daily	1 mL twice daily
(b) (4)		
4 (b) (4) to less than 6.0	30 mg twice daily	1.5 mL twice daily
6.0 to less than (b) (4)	40 mg twice daily	2 mL twice daily
(b) (4)		
11 (b) (4) to less than 14.0	80 mg twice daily	4 mL twice daily
14.0 to less than 20.0	100 mg twice daily	5 mL twice daily

The current applications fulfill one of the two outstanding post-marketing requirements (PMR) under Pediatric Research Equity Act (PREA):

> 'Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients 4 weeks to less than 2 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a

minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.'

The PREA PMR was fulfilled for ages 2 to 18 years of age previous submissions to NDA 22145 and 203045.

3. CMC

Please refer to ONDQA's Chemistry review by Dr. Chunchun Zhang and Biopharmaceutics review by Dr. Kareen Riviere for full details. In summary, issues related to stability, microbial testing, and product quality have been adequately addressed by the Applicant. An overall recommendation of Acceptable has also been made by the Office of Compliance. The NDA submission does not include a dissolution method report or a proposed dissolution acceptance criterion because the Applicant believes a dissolution test is not needed for the proposed product. However, the ONDQA Biopharmaceutics team requested that the Applicant include a drug release test in the drug product specification. This information request has been satisfactorily addressed.

NDA 205786 provides data for raltegravir oral (b) (4) Suspension (b) (4). The formulation is similar to the chewable tablet formulation, containing sweeteners and flavors for taste masking. The drug product has a shelf life of 24 months at controlled room temperature. GFS is supplied as a kit holding 60 unit dose sachets (each sachet containing equivalent of 100mg raltegravir), (b) (4) mixing cup and 2 oral dosing syringes. Each sachet is for single use. After mixing the granules with water, the desired suspension is to be delivered via dosing syringe and the remaining unused suspension is to be discarded.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data was submitted. Refer to the original NDA submission for details.

5. Summary of Pharmacokinetic Data

Two clinical studies were conducted and submitted for review- P068 and P1066.

Trial P068 evaluated the relative bioavailability of raltegravir when administered using film-coated tablets (reference) and chewable tablets (test) or GFS (test) to healthy adults. Trial results demonstrated that raltegravir chewable tablets and GFS were not bioequivalent to reference film-coated tablets. The study demonstrated increased bioavailability and rapid absorption of the GFS formulation compared to the poloxamer (film-coated) formulation and the pediatric chewable tablet formulation. In addition, the GFS formulation demonstrated a 4-folder increase in AUC and 2-fold increase in Cmax compared to the film-coated tablets. As such, the raltegravir GFS formulation was not bioequivalent with the previously approved film-coated tablets or chewable tablets. Similarly, mean raltegravir $AUC_{0\text{-}inf}$ and C_{max} values were 78% and 222% higher, respectively, with chewable tablets compared to reference tablets.

Based on results from trial P068, it was concluded that raltegravir film-coated tablets, chewable tablets and GFS are not bioequivalent and should not be used interchangeably at the same dose.

	AUC (μM*hr)	Cmax (nM)	C12h (nM)	Tmax (hr)	T1/2 (hr)
Oral Tablets	19.2	5	149	4	9
Chewable Tablets	34.2	16.1	134	0.5	9.3
GFS	50.4	23.2	162	1	10

P1066 which is currently ongoing, is a Phase 1/2, multi-center, open-label, non-comparative trial to evaluate the safety and antiviral activity of raltegravir in approximately 140 HIV-1 infected children 4 weeks to 18 years of age. Raltegravir was administered as the film-coated tablets, chewable tablets or GFS formulation. The GFS formulation was evaluated in subjects less than 2 years of age. The pharmacokinetic, safety and efficacy data in children 2 years and older were previously reviewed in detail by Drs. Tafadzwa Vargas-Kasambira (Clinical) and Ruben Ayala (Clinical Pharmacology). Please refer to the respective reviews for additional details.

The current submission contains PK, safety and efficacy data for the GFS formulation. Please refer to reviews by Drs. Brittany Goldberg (Clinical) and Fang Li (Clinical Pharmacology) for full details. Additional long-term safety data for subjects 2 years of age and older was also submitted for review. The main pharmacokinetic, safety and efficacy results are addressed in this CDTL review.

- **Summary of Important Clinical Pharmacology and Biopharmaceutics Finding (P1066)**

This submission contains data from IMPAACT P1066, an ongoing Phase I/II multi-center, open-label, non-comparative study containing pharmacokinetic data, as well as Week 24 and 48 safety and efficacy data from 26 HIV-infected infants and toddlers (4 weeks to <2 years). Subjects were stratified by age, and all received weight-based raltegravir GFS dosing. All doses of raltegravir were administered in combination with other antiretroviral medications.

Cohort IV: ≥6 months to <2 years old; received raltegravir 6 mg/kg BID.

Cohort V: ≥4 weeks to <6 months old; received raltegravir 6 mg/kg BID.

The trial was divided into Stage 1 and 2. The initial dose-finding period enrolled subjects from Cohort IV who underwent intensive PK sampling (Stage 1).

The PK/PD or exposure-response analyses conducted during the original adult Phase 2 and 3 trials did not identify specific pharmacokinetic parameters that correlated with efficacy outcomes. Use of additional active agents in optimized background therapy (OBT) and baseline HIV RNA levels were predictive of efficacy outcome. The influence of raltegravir concentrations on treatment outcome was most evident for subjects with very limited or no active optimized background therapy (OBT). Therefore, the goal of the pediatric dose selection was to target the adult exposure (AUC_{12}) with 400 mg BID, which is known to be an effective dose.

A pediatric dose of 6mg/kg, which was anticipated to achieve similar AUC to 400 mg BID in an adult patient weighing 70 kg, was selected. The pediatric dose was also selected to achieve the following pharmacokinetic targets:

- AUC_{12}

  Maintain a raltegravir geometric mean (GM) AUC_{12} between 14 and 25 μM*hr, with individual AUC 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.

- C_{12}

  Maintain GM raltegravir C_{12} >33 nM, which corresponds to the *in vitro* IC95 for antiviral activity. Of note, in the original adult Phase 2 and 3 trials, the relationship between C_{12} and HIV RNA <50 copies/mL was shallow (see discussion under Efficacy). Raltegravir 800mg once daily was recently evaluated in HIV infected adults. Emergent PK/PD data from this study (raltegravir 400 mg BID vs. raltegravir 800 mg QD in treatment-naïve HIV infected adults, also known as QDMRK) failed to demonstrate the non-inferiority of the 800 mg QD to the 400mg BID arm. This suggested that there were relationships between raltegravir trough concentrations and efficacy not evident in previous adult BID dose ranging studies. These data suggested that Ctrough values below 45nM were associated with a higher probability of virologic failure. By the time this information became available, the pediatric trial was well underway with the selected dose (6mg/kg) to maintain GM raltegravir C_{12} >33 nM.

The arithmetric mean raltegravir exposures (AUC12 and C12) are summarized in the table below. The mean AUC values in pediatric subjects fell within the target range of 14 to 25 μM*hr (range, 15.7 to 22.6 μM*hr). All mean C_{12} values exceeded the target of >33 nM. All mean C12 also exceeded 45 nM.

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

In summary, based on the results above, it can be concluded that the doses selected are appropriate and achieve the targeted exposures observed in adults at the approved raltegravir dose of 400 mg twice daily. However, as further discussed in Section 6 (under 'Formulations'), for some weight bands where more than one dosing formulation is available, the tablet or the GFS formulations may lead to higher Ctrough concentrations compared to the chewable formulation.

6. Efficacy Evaluation

This section summarizes the efficacy analyses from trial P1066 supporting our decision to expand the indication for raltegravir. Please refer to reviews by Drs. Brittany Goldberg and Fang Li for additional clinical and clinical pharmacology discussions, respectively.

- **Trial Design**

Trial P1066 evaluated the pharmacokinetics, safety and antiviral activity (efficacy) of raltegravir in treatment-experienced pediatric subjects 4 weeks to < 19 years of age with HIV-1 infection. Raltegravir is administered orally as a film-coated tablet, chewable tablet, or oral granules for suspension (GFS) in water. This submission reviews the use of raltegravir as GFS in children aged ≥4 weeks to < 2 years. Subjects were stratified by baseline HIV RNA (< vs. ≥ 100,000 copies/mL)

The primary efficacy endpoint for this trial was plasma viral load < 50 copies/mL and <400 copies/mL at Week 24 and 48. Although the FDA's efficacy analysis is based on the Snapshot algorithm, the Applicant used the Observed Failure and Non-Completer approaches to handle missing data.

- **Results**

Twenty-six subjects were enrolled in the study and received raltegravir. The median age was 6.8 months (range 0.98 to 23.1), with a male predominance (66.7%) and the majority of subjects were black (85.2%). Most subjects (85%) had baseline HIV RNA ≥ 100,000 copies/mL. While all had previous ARV treatment history, only 2 subjects had history of exposure to three or more ARVs. Most (77%) had PSS and GSS score of 2 or greater.

While 26 subjects enrolled, three subjects in Cohort V were enrolled to provide supplemental pharmacokinetic data and had not yet reached Week 24. Therefore, the efficacy analysis is based on the 23 remaining subjects.

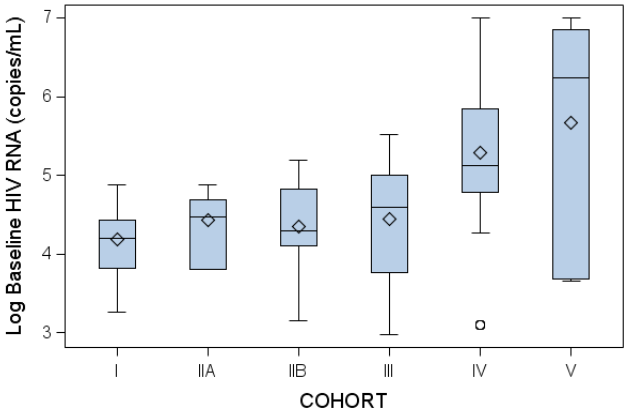
The key primary efficacy results (by snapshot algorithm) are summarized in the table below. At Week 24, the proportion of subjects with HIV RNA < 50 copies/mL and <400 copies/mL were 39% and 61%, respectively. The proportion of subjects considered virologic failures (HIV RNA >400 copies/mL) was 35% (8/23); in addition, 57% (13/23) had HIV RNA >50 copies/mL.

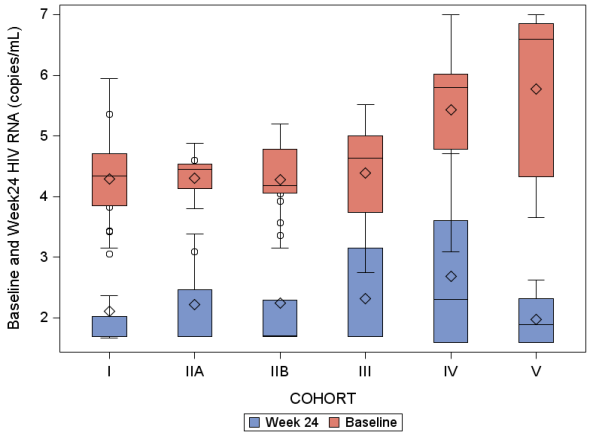
Virologic outcome at Week 24 based on snapshot algorithm

Virologic Outcome n, (%)	**Raltegravir GFS N=23**
Virologic Success (HIV RNA <50 copies/mL)	9/23 (39.1)
Virologic Failures (HIV RNA ≥ 50 copies/mL),	13/23 (56.5)
No Virologic Data at 24 Week Window	
Discontinued trial/trial drug due to AE or death*	1/23 (4.3)
Discontinued trial/trial drug for Other Reasons	0/23
Missing data during window but on study	0/23

The efficacy outcome at Week 48 was generally similar to Week 24. The proportion of subjects with HIV RNA < 50 copies/mL was 44%; and 61% had HIV RNA < 400 copies/mL. Additionally, 26% and 44% had HIV RNA ≥400 and 50 copies/mL, respectively.

The efficacy rate of raltegravir was somewhat lower in these two youngest age cohorts compared to the older age cohorts or adults. The proportion of older pediatric subjects with HIV RNA < 50 and <400 copies/mL at Week 24 were 53% (51/96) and 66%, respectively; the efficacy (HIV RNA < 50 copies/mL) demonstrated at Week 24 in the treatment experienced adult trials (BNCHMRK 1 and 2) was 63%. Additional analyses were conducted to identify a factor contributing to the lower efficacy rate in the younger age cohorts. Among the factors considered were lower exposures and baseline characteristics. As discussed above, the exposures were considered adequate. Baseline HIV RNA was also considered as a factor. Compared to the older age groups, baseline HIV RNA was significantly higher in Cohorts IV and V, as shown in the figures below. Although small sample size, the response rate is higher in subjects with baseline HIV RNA <100,000 copies/mL; the proportion of subjects with HIV RNA <50 copies/mL were 63% (5/8) and 26% (4/15) among subjects with baseline HIV RNA < vs. ≥100,000 copies/mL, respectively. Nonetheless, HIV log reductions were shown for all subjects, regardless of baseline HIV RNA; in fact, those with highest baseline viral load (i.e. Cohorts IV and V) had the greatest log decrease during the first 24 weeks of treatment (figure to the right).





Subgroup Analyses

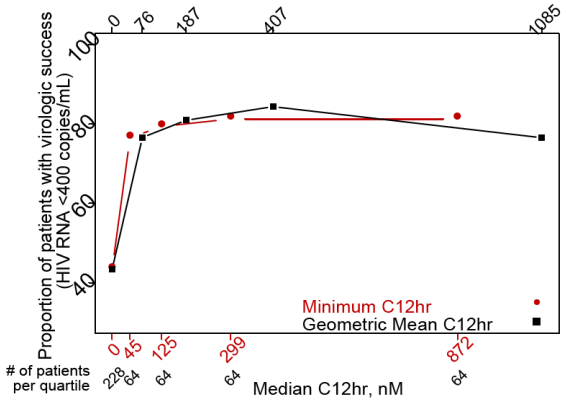
The number of subjects enrolled is too few to conduct any meaningful analyses on the relationship between age, race, baseline CD4 counts and efficacy outcome. Such relationships were not established in adults.

Exposure-response Analyses

In the original adult clinical trials, the association between raltegravir GM C_{12} and antiviral response was shallow, as demonstrated in the figure below. Raltegravir displayed no clinically significant difference in virologic success rates across a wide range of C_{12} values measured in treatment-experienced adults receiving 400 mg BID. Within the concentration range studied, the virologic success rates were (77%) for subjects with lower C_{12} values (76 nM) compared

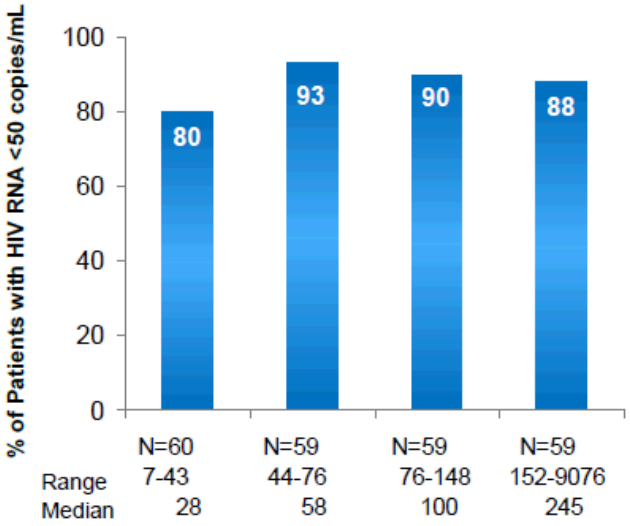
to those with higher C_{12} values (1085 nM). Therefore, no specific adult C_{12} value was targeted for pediatric subjects. The goal for the pediatric GM C_{12} exposure was to deliver trough values greater than the in vitro IC_{95} value (i.e. the inhibitory concentration).

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



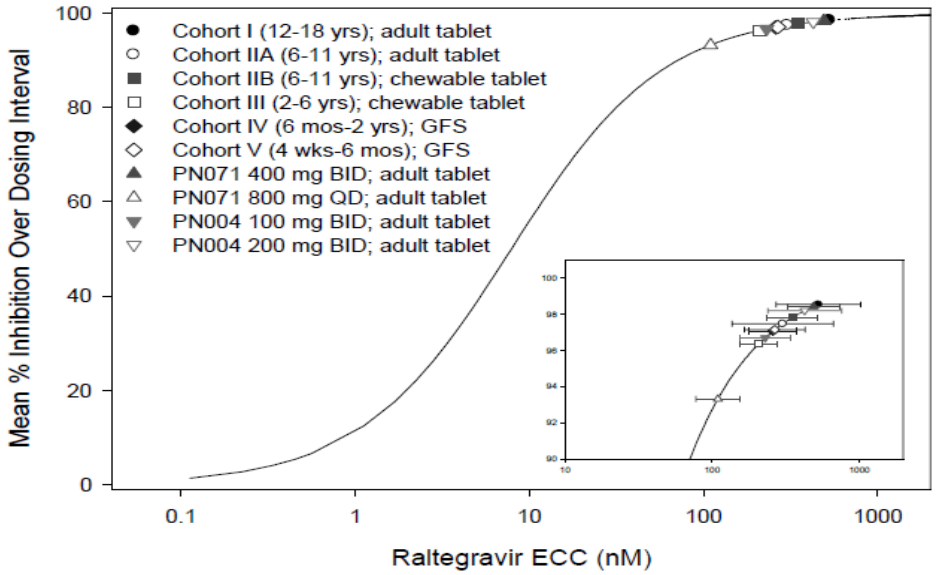
Source: Clinical Pharmacology Review

However, based on the data from the once daily raltegravir trial (800mg QD), PK/PD relationships appear to exist between Ctrough and virologic response (see section 5 above). Recent data from Study 071 comparing raltegravir 400 mg BID vs. 800 mg QD have suggested a PK/PD relationship with Ctrough, where low Ctrough (<45 nM) in the 800 mg QD arm was associated with a higher probability of virologic failure. Results of a quartile analysis shows lower efficacy in subjects in the lowest quartile of Ctrough.

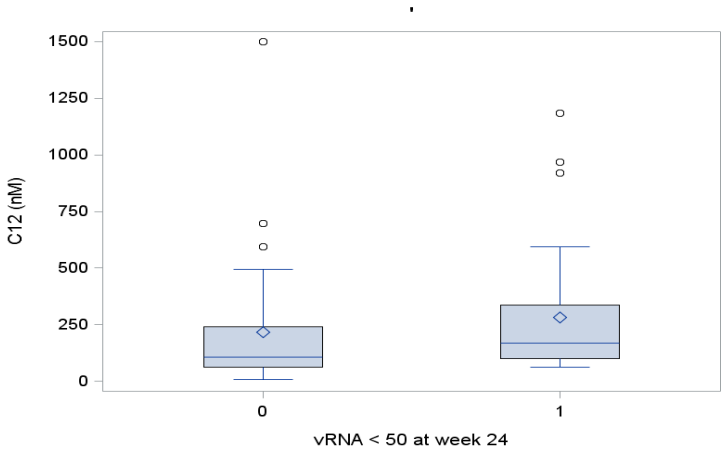


For the pediatric trial, the Applicant constructed a PK/PD viral dynamics model to evaluate PK/PD relationship of raltegravir and viral inhibition using Equivalent Constant Concentration (ECC) and percent of viral inhibition. The Applicant used this approach to calculate an ECC value for the observed PK profiles in pediatric subjects and compared the results to the adult 400mg BID and 800mg QD dosing regimens. For comparisons, raltegravir 800 mg QD, which

did not demonstrate noninferiority to raltegravir 400 mg BID, has a predicted GM ECC value of 49 ng/mL and the lowest percent viral inhibition of all the regimens. In contrast, GM ECC values of the pediatric cohorts all exceeded the ECC predicted for 800 mg QD. The ECC and viral inhibition relationship are displayed in the figure below.



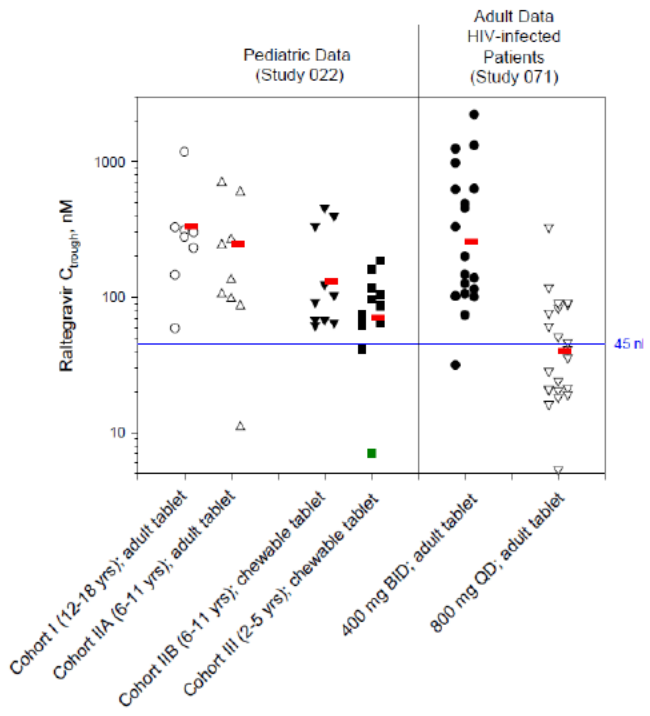
In addition, as demonstrated in the figure below, the Ctrough concentrations in pediatric subjects who were virologic failures (designated as '0' in the figure below) were lower compared to subjects who had virologic success ('1').

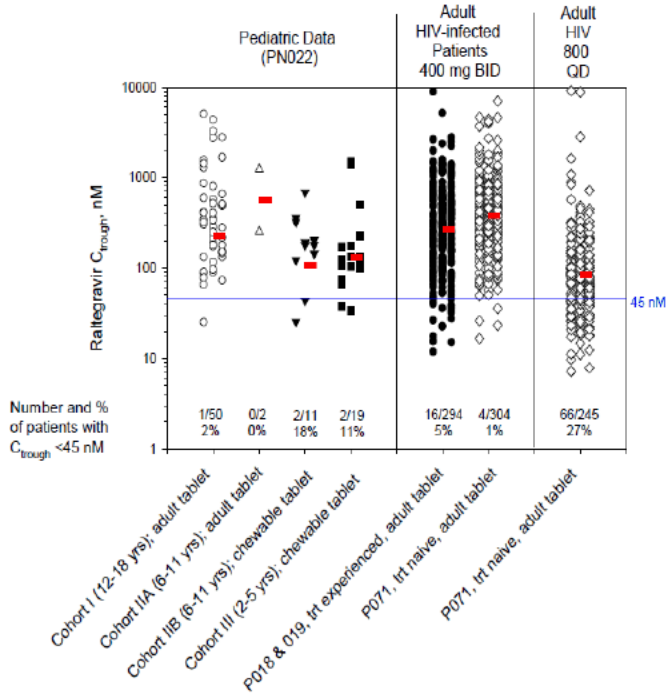


Formulation

Raltegravir chewable tablets or film-coated tablets have been approved for children 2 years of age and older since 2011. As described above, the PK/PD data supporting Ctrough of 45nM as the minimal effective exposure has been recently identified. With this emergent PK information, additional evaluations were conducted by the Applicant to compare the intensive and sparse PK data from the pediatric trial, grouped by formulation and treatment cohort, to the adult BID and QD (QDMRK) data. As shown in the figures below, the mean trough exposure in pediatric cohorts who received the chewable tablet formulation is lower than the

tablet formulation. Therefore, labeling recommendations have been made to allow for preferred usage of the film-coated formulation. In addition, the Dosage and Administration section and Clinical Pharmacology section have been modified to display the information by weight (b) (4). This modification recommends the tablet formulation as the preferred formulation for patients weighing at least 25 kg, regardless of age. For patients weighing 11 to 20 kg, both the chewable and the GFS formulations are recommended because the chewable tablet may offer ease of administration and convenience compared to the GFS. However, it is noted that the lowest trough concentrations were observed with the chewable tablet.





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The following is the proposed dosing recommendations by the Division for all pediatric patients:

Section 2 (Dosage and Administration)

- **If at least 25 kg:** One 400 mg film-coated tablet orally, twice daily.
  If unable to swallow a tablet, consider the chewable tablet, as specified in Table 1.

Table 1: Alternative** Dose with ISENTRESS Chewable Tablets for Pediatric Patients Weighing at Least 25 kg

Body Weight (kg)	Dose*	Number of Chewable Tablets
25 to less than 28	150 mg twice daily	1.5 x 100 mg† twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily

**See Section 12 Clinical Pharmacology

*The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

†The 100 mg chewable tablet can be divided into equal halves.

- **If at least 3 kg to less than 25 kg:** Weight based dosing, as specified in Table 2. For patients weighing between 11 and 20 kg, either the chewable tablet or (b) (4) suspension can be used, as specified in Table 2.

Table 2: Recommended Dose* for ISENTRESS (b) (4) Suspension and Chewable Tablets in Pediatric Patients Weighing Less than 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	
4 to less than 6	1.5 mL (30 mg) twice daily	
6 to less than 8	2 mL (40 mg) twice daily	
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25	-	1.5 x 100 mg‡ twice daily

*The weight-based dosing recommendation for the chewable tablet and (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily.
†For weight between 11 and 20 kg either formulation can be used; see Section 12, Clinical Pharmacology
Note: The chewable tablets are available as 25 mg and 100 mg tablets.
‡The 100 mg chewable tablet can be divided into equal halves.

Section 12 (Clinical Pharmacology)

Pediatric

Two pediatric formulations were evaluated in healthy adult volunteers, where the chewable tablet and granules for suspension were compared to the 400 mg tablet. The chewable tablet and granules for suspension demonstrated higher oral bioavailability, thus higher AUC, compared to the 400 mg tablet. In the same study, granules for suspension resulted in higher oral bioavailability compared to the chewable tablet. These observations resulted in proposed pediatric doses targeting 6 mg/kg/dose for the chewable tablets and (b) (4) suspension. As displayed in Table 9, the doses recommended for HIV-infected infants, children and adolescents 4 weeks to 18 years of age *[see Dosage and Administration (2.3)]* resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily.

Overall, dosing in pediatric patients achieved exposures (C_{trough}) above 45 nM in the majority of subjects, but some differences in exposures between formulations were observed. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations (113 nM) compared to pediatric patients above 25 kg administered the 400 mg tablet formulation (233 nM) *[see Clinical Studies (14.3)]*. As a result, the 400 mg film-coated tablet is the recommended dose in patients weighing at least 25 kg; however, the chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the film-coated tablet *[see Dosage and Administration (2.3)]*. In addition, pediatric

patients weighing 11 to 25 kg who were administered the chewable tablets had the lowest trough concentrations (82 nM) compared to all other pediatric subgroups.

. **Table 9: Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses**

Body Weight	Formulation	Dose	N*	Geometric Mean (%CV†) $AUC_{0\text{-}12hr}$ (μM•hr)	Geometric Mean (%CV†) C_{12hr} (nM)
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (b) (4))	233 (b) (4))
≥25 kg	Chewable tablet	Weight based dosing, see Table 1	9	22.1 (*36%*)	113 (b) (4))
11 to less than 25 kg	Chewable tablet	Weight based dosing, see Table 2	13	18.6 (b) (4))	82 ((b) (4))
3 to less than 20 kg	Granules for suspension	Weight based dosing, see Table 2	19	24.5 (b) (4))	113 (b) (4))

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Coefficient of variation.

7. Safety Evaluation

This section summarizes the major safety findings from study P1066. In general, Dr. Goldberg's independent analyses of the safety data confirmed Merck's findings. The Division is in agreement with the safety labeling as proposed by the Applicant.

- **Adequacy of Safety Database**

The safety assessments in 26 subjects 4 weeks to 2 years of age were considered sufficient, as safety data already exists in adults and other pediatric subpopulations (i.e. children >2 years of age). In addition, the Applicant has enrolled sufficient number of subjects across the age groups, in accordance to the general recommendations routinely made by the Division. In addition, long-term safety data for pediatric subjects older than 2 years of age has also been submitted with this application

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

The data submitted supports the safety and tolerability of raltegravir in pediatric subjects when administered in combination with other ARVs. The Applicant has submitted safety data for 26 pediatric subjects who received the to-be-marketed dose (final dose, FD) for 24 to 48 weeks.

As with most pediatric HIV trials, this clinical trial did not have an active comparator arm. Therefore, the results discussed below have some limitations. Refer to Dr. Goldberg's review for additional details.

There were no deaths reported during the 48 weeks of the study period. However, one subject died due to gastroenteritis at Week (b) (6). The cause of death was not attributed to the

study drug by the Applicant. Overall, nine subjects experienced one or more treatment-emergent serious adverse events (clinical or laboratory) during the 48 weeks of the study period. One clinical event (non-laboratory related) was considered to be treatment-related. This was a Grade 3 rash, which led to treatment discontinuation. The laboratory -related SAE include anemia (Grade 4), elevated lipase (Grade 4) and elevated bilirubin (Grade 3). None led to treatment discontinuation. The elevation in lipase was not associated with clinical pancreatitis; the subject with elevated bilirubin did not have jaundice or hepatomegaly and the liver serum biochemistries did not meet Hy's Law criteria; the event was considered to be treatment-related.

One subject discontinued treatment due to an adverse event. The subject experienced Grade 3 rash ('erythematous rash') on Day 6, considered to be treatment-related.

The majority of the adverse events reported during the trial were grade 1 or 2 in severity. The most commonly reported treatment-emergent adverse events were rash (77%), cough (77%) and rhinorrhea (65%).

Adverse events of interest identified with previous trials included immune reconstitution syndrome (IRIS), rash, AST/ALT elevations (hepatobiliary events), and psychiatric disorders. Due to the nature of the current cohorts (i.e. age), no psychiatric adverse events were reported.

Rash: Rash was reported in 20 (77%) subjects during the trial, including 15 cases of 'rash', 1 case of 'rash erythematous', 5 cases of 'rash generalized', 2 cases of 'erythema', 2 cases of 'eczema', 1 'drug eruption' and 8 cases of 'dermatitis'. The subject with erythematous rash/drug eruption discontinued treatment due to the event (Grade 3), as described above. All other episodes of rash were considered mild or moderate.

Hepatic-related clinical events were not reported during the trial. However, many subjects (~50%) were noted to have AST and/or ALT elevations; most were grade 1 or 2; one subject had grade 3 increase in ALT. Of note, this subject had the worse grade toxicity at Week 0 and follow-up labs showed resolution of the elevation; the study drug was not discontinued.

IRIS: One subject developed immune reconstitution syndrome (IRIS) due to *M. bovis* while on therapy and recovered by Week 24 without interruption of study treatment. The subject discontinued from the trial at week 36 due to moving.

The majority of treatment-emergent laboratory abnormalities were reported as grade 1 or 2. Grade 3 or 4 laboratory abnormalities included elevated lipase (grade 4, 1 subject), elevated ALT (grade 4, 1 subject), elevated total bilirubin (grade 3, 1 subject), decreased hemoglobin (grade 3 or 4, 2 subjects), and neutropenia (grade 3, 2 subjects). None led to treatment discontinuation.

In summary, the adverse event, both types and frequency, reported in these cohorts are generally similar to those observed in older children or adults. These events are adequately described in Section 6 of the USPI. Based on the data reviewed, no other additional recommendations are warranted to section 6 of the USPI.

8. Labeling

Package Insert

The following revisions to the Dosing and Administrations and Clinical Pharmacology sections of the USPI have been proposed and are under negotiations:

Pediatrics

- **If at least 25 kg:** One 400 mg film-coated tablet orally, twice daily.
  If unable to swallow a tablet, consider the chewable tablet, as specified in Table 1.

Table 1: Alternative Dose* with ISENTRESS Chewable Tablets for Pediatric Patients Weighing at Least 25 kg

Body Weight (kg)	Dose	Number of Chewable Tablets
25 to less than 28	150 mg twice daily	1.5 x 100 mg† twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily
The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily. [*See Clinical Pharmacology (12.3)*] †The 100 mg chewable tablet can be divided into equal halves.		

- **If 4 weeks of age and weighing at least 3 kg to less than 25 kg:** Weight based dosing, as specified in Table 2.
  For patients weighing between 11 and 20 kg, either the chewable tablet or (b) (4) suspension can be used, as specified in Table 2.

Table 2: Recommended Dose* for ISENTRESS (b) (4) Suspension and Chewable Tablets in Pediatric Patients Weighing Less than 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	
4 to less than 6	1.5 mL (30 mg) twice daily	
6 to less than 8	2 mL (40 mg) twice daily	
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25	-	1.5 x 100 mg‡ twice daily

*The weight-based dosing recommendation for the chewable tablet and (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily. [*See Clinical Pharmacology (12.3)*]
†For weight between 11 and 20 kg either formulation can be used.
Note: The chewable tablets are available as 25 mg and 100 mg tablets.
‡The 100 mg chewable tablet can be divided into equal halves.

Section 12 (Clinical Pharmacology)

Pediatric

Two pediatric formulations were evaluated in healthy adult volunteers, where the chewable tablet and (b) (4) suspension were compared to the 400 mg tablet. The chewable tablet and (b) (4) suspension demonstrated higher oral bioavailability, thus higher AUC, compared to the 400 mg tablet. In the same study, (b) (4) suspension resulted in higher oral bioavailability compared to the chewable tablet. These observations resulted in proposed pediatric doses targeting 6 mg/kg/dose for

the chewable tablets and [redacted] suspension. As displayed in Table 9, the doses recommended for HIV-infected infants, children and adolescents 4 weeks to 18 years of age *[see Dosage and Administration (2.3)]* resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily.

Overall, dosing in pediatric patients achieved exposures (C_{trough}) above 45 nM in the majority of subjects, but some differences in exposures between formulations were observed. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations (113 nM) compared to pediatric patients above 25 kg administered the 400 mg tablet formulation (233 nM) *[see Clinical Studies (14.3)]*. As a result, the 400 mg film-coated tablet is the recommended dose in patients weighing at least 25 kg; however, the chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the film-coated tablet *[see Dosage and Administration (2.3)]*. In addition, pediatric patients weighing 11 to 25 kg who were administered the chewable tablets had the lowest trough concentrations (82 nM) compared to all other pediatric subgroups.

Table 9: Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses

Body Weight	Formulation	Dose	N*	Geometric Mean (%CV†) $AUC_{0\text{-}12hr}$ (μM•hr)	Geometric Mean (%CV†) C_{12hr} (nM)
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 [redacted])	233 [redacted]
≥25 kg	Chewable tablet	Weight based dosing, see Table 1	9	22.1 (*36%*)	113 [redacted]
11 to less than 25 kg	Chewable tablet	Weight based dosing, see Table 2	13	18.6 [redacted])	82 [redacted]
3 to less than 20 kg	Granules for suspension	Weight based dosing, see Table 2	19	24.5 [redacted])	113 [redacted])

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Coefficient of variation.

Patient Package Insert

Routine consultation to the Patient Labeling Team (PLT) and OPDP were requested and recommendations have been provided. The recommendations to the label are currently under negotiations. The primary content of the recommendations are formatting and reorganization of the information contained within the PPI. In addition, the new IFU submitted with the proposed label was reviewed and recommendations have been made.

9. Outstanding Issues

At this time, negotiations for the USPI are still ongoing.

10. Recommendations/ Risk Benefit Assessment

I recommend the approval of this pediatric application. The data from the current NDA provide sufficient pharmacokinetic evidence to recommend raltegravir twice daily dosing, co-administered with other ART for the treatment of HIV-1 infection in pediatric patients 4 weeks [redacted]

(b) (4). The final dose selected and administered led to mean AUC exposures that were comparable to the targeted adult mean AUC. The mean Ctrough concentrations observed were also above the targeted exposure of 33 nM or 45 nM.

Results from P1066 demonstrated that raltegravir was an effective treatment in suppressing HIV RNA (<50 copies/mL and <400 copies/mL). In this treatment experienced population, the overall the proportion of subjects with HIV RNA < 50 copies/mL and <400 copies/mL at Week 24 were 39% and 61%, respectively. The apparent lower rate of response (HIV RNA <50 copies/mL) was primarily due to the higher baseline viral load observed in Cohorts IV and V.

Raltegravir GSF was generally safe and well tolerated; one subject discontinued trial due to rash. The long-term safety data for the older pediatric subjects revealed no new significant safety events. Overall, across the pediatric age groups studied, there were neither new safety signals identified nor were there major safety differences identified between pediatric subjects and adults.

11. Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

YODIT BELEW
12/12/2013