CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203045Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 9, 2011
From	Yodit Belew, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/NDA # **Supplement #**	NDA 203045 sNDA 22145 (S-022)
Applicant	Merck
Date of Submission	June 30, 2011
PDUFA Goal Date	December 30, 2011
Proprietary Name / Established (USAN) names	Isentress(raltegravir)
Dosage forms / Strength	New proposed dosage formulation: chewable tablets/ 25mg, 100mg Approved dosage form: film-coated tablets/400 mg
Proposed Indication(s)	Treatment of HIV infection in children 2 to 18 years of age
Recommended:	Approval

1. Introduction

This review summarizes the main issues for Merck's NDAs seeking approval of Isentress (raltegravir) for treatment of HIV-1 infection in pediatric patients 2 to 18 years of age. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data. 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 new chewable tablets were evaluated in the current pediatric NDA submissions. The application extends the intended population to 2 years of age and weighing at least 10 kg: adolescents (12 to 18 years of age) and children 6 to less than 12 years of age and weighing at least 25 kg would take the 400mg film-coated tablets twice daily, while children 6 to less than 12 years of age weighing less than 25 kg and children 2 to less than 6 years of age would take chewable tablet formulation using a weight based dosing. Unfortunately, the film-coated and the chewable tablets are not bioequivalent, thus are not interchangeable. This application was granted a priority review as it pertains to pediatric population.

2. Background

Raltegravir, an inhibitor of the catalytic activity of HIV-1 integrase, was originally approved in October, 2007. It is the first and only drug in its class currently approved for treatment of HIV infection. Raltegravir is an important product for adult patients receiving antiretroviral treatment for HIV infection, as it is recommended as a preferred drug for constructing an integrase inhibitor based regimen when initiating ART treatment in treatment naïve adults. The recommended dose of raltegravir in treatment naïve and experienced adult patients is 400 mg of the film-coated tablets, taken twice daily.

Two NDA applications were submitted in support of raltegravir dosing in children 2 to 18 years of age: sNDA 22145 (SN 022) and NDA 203045. A new NDA (203045) was created because a new chewable tablet was formulated. Data from children 2 to less than 12 years of age who were administered the chewable formulation was submitted to this NDA while the data for children 6 to 18 years of age who were administered the film-coated tablet were submitted to NDA 22145. The proposed dosing regimen for pediatric patients 2 to 18 years of age is as follows:

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 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)
10 to <14	22 to <31	75 mg twice daily	3 X 25 mg
14 to <20	31 to <44	100 mg twice daily	1 X 100 mg
20 to <28	44 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.

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 2 to less than 18 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.'
Requirement/commitment Number 2 under NDA 22145.

The PREA PMR was fulfilled for ages 6 to 18 years of age and for 2 to less than 12 years of age with the current submissions to sNDA 22145 and NDA 203045, respectively.

3. CMC

Please refer to ONDQA's review by Dr. Andrew Yu and Biopharmaceutics review by Dr. Arzu Selen for full details. In summary, issues related to stability, microbial testing, and product

quality have been adequately addressed by the Applicant. A recommendation of approval has been made by ONDQA.

NDA 203-045 provides data for raltegravir chewable tablets, 100 mg and 25 mg, for pediatric use. The 25 mg strength is an un-scored round-shaped tablet while the 100 mg strength is a scored oval-shaped tablet to allow dosing of 50 mg. The two chewable tablet strengths (25 mg and 100 mg) may be used interchangeably. They can also be chewed or swallowed as whole. The currently approved raltegravir tablet (film-coated 400 mg strength) can only be swallowed as whole.

The chewable tablet formulations contain sweeteners and flavors for taste masking and other commonly used excipients for tablet formulations. Among the excipients is aspartame, which is hydrolyzed into phenylalanine in the gut. Per 21 CFR 201.21 (C) 'The package labeling and other labeling providing professional use information concerning prescription drugs for human use containing aspartame as an inactive ingredient shall bear a statement to the following effect under the "Precautions" section of the labeling, as required in §201.57(f)(2): Phenylketonurics: Contains Phenylalanine (_)mg Per (Dosage Unit).' Therefore, a new section ('Section 5.3 Phenylketonurics') has been added to the Warnings and Precautions section of the USPI to reflect the presence of aspartame. Similar information has been included in Section 17 and in the PPI.

4. Nonclinical Pharmacology/Toxicology

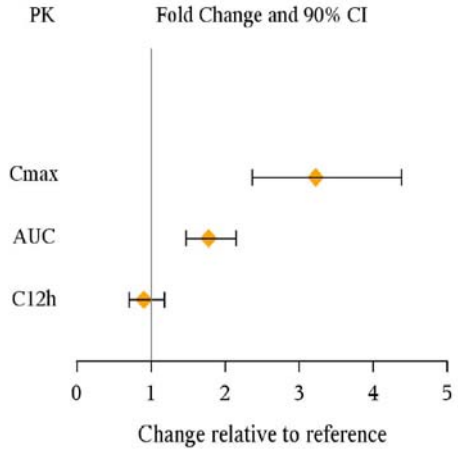
No new nonclinical pharmacology/toxicology data was submitted. Refer to the original NDA submission for details.

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) to healthy adults. Trial results demonstrated that raltegravir chewable tablets were not bioequivalent to reference film-coated tablets. Mean raltegravir $AUC_{0\text{-}inf}$ and C_{max} values were 78% and 222% higher, respectively, with chewable tablets compared to reference tablets following a single 400 mg dose (Figure 1). On the other hand, raltegravir C_{12h} values were similar for both formulations. Based on results from trial P068, it was concluded that raltegravir film-coated and chewable tablets are not bioequivalent and should not be used interchangeably at the same dose.

Figure 1: Exposure differences between Chewable (test) vs. Film-Coated (reference)



Source: Dr. Ruben Ayala, Clinical Pharmacology

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 or chewable tablets formulation. A third formulation, oral granules for suspension in water, is available for subjects less than 2 years of age. (b) (4) The pharmacokinetic, safety and efficacy data are discussed in details in the Clinical Review by Dr. Tafadzwa Vargas-Kasambira and in the Clinical Pharmacology Review by Ruben Ayala (Pharm.D). Please refer to the respective reviews for additional details. The main pharmacokinetic, safety and efficacy results are addressed in this review.

Summary of Important Clinical Pharmacology and Biopharaceutics Finding (P1066)

One hundred and twenty six (126) subject ages 2 to 18 years of age were enrolled for this submission; of those, 96 received the final selected doses (final dose, FD) of raltegravir. Subjects were stratified by age, and raltegravir was administered as the film-coated tablets or 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: ≥12 to 18 years old; received raltegravir 400 mg BID using film-coated tablets.

Cohort 2a: ≥6 to <12 years old; received raltegravir 400 mg BID using film-coated tablets.

Cohort 2b: ≥6 to <12 years old; received raltegravir 6 mg/kg BID using chewable tablets.

Cohort 3: ≥2 to <6 years old; received raltegravir 6 mg/kg BID using chewable tablets.

The trial was divided into Stage 1 and 2. The initial dose-finding period enrolled 58 subjects who underwent intensive PK sampling (Stage 1).

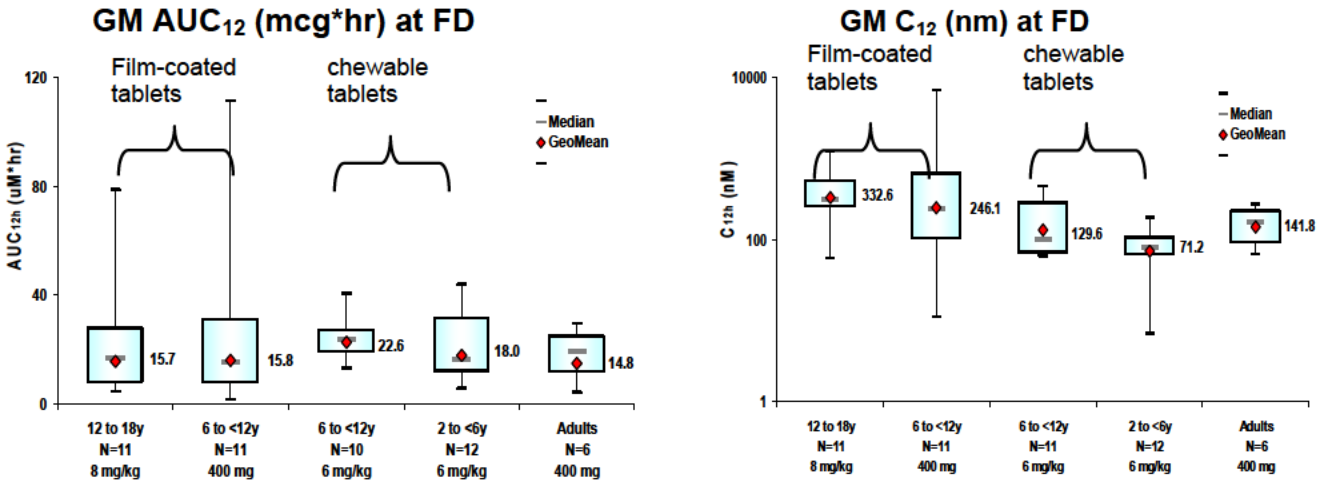
The PK/PD analyses or exposure-response analyses conducted during the adult Phase 2 and 3 trials did not identify any specific pharmacokinetic parameter that correlated with efficacy outcomes. Use of additional active agents in optimized background therapy (OBT) and baseline HIV RNA levels were the predictive 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}) from the 400 mg BID, which is known to be an effective dose.

An initial pediatric dose of 6mg/kg, which is approximately equivalent to 400 mg BID in adult patient weighing 70 kg, was selected. The pharmacokinetic targets were:

- 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 *in vitro* IC95 for antiviral activity. Of note, in the adult trials, the relationship between C_{12} and HIV RNA <50 copies/mL was shallow (see discussion under Efficacy).

Pharmacokinetic results from stage 1 were as follows:

Figure 2 GM AUC and trough at the Final Dose (FD)



All GM AUC_{12} values fell within 14 to 25 uM*hr

All GM C12 values were greater than 33 nM (IC95)

Source: Dr. Ruben Ayala, Clinical Pharmacology

As summarized in the figures above, 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.

When the pediatric exposures of raltegravir were compared to that in adults, the mean exposures (AUC_{12}) among the pediatric cohorts were within 80 to 115% of the relative mean adult exposures. In other words, the highest and lowest mean exposures observed in pediatric subjects were 15% higher and 20% lower than the mean adult exposure. This is within the generally accepted range of exposure that DAVP targets for pediatric drug development.

In addition, the following conclusions were made based on the intensive PK data:

- There were similar exposure by age and weight at the final proposed doses
- 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
- Mean raltegravir exposures (AUC_{12} and C_{12}) were similar across males and females receiving the final dose per cohort
- Significant inter-subject PK variability was observed across all cohorts, higher in subjects using the film-coated tablets

In summary, based on the results above, one can conclude that the doses selected for the Final Dose population were appropriate and approximated the targets in adults at the approved raltegravir dose of 400 mg twice daily.

6. Efficacy Evaluation

Trial P1066 evaluated the pharmacokinetics, safety and antiviral activity (efficacy) of raltegravir in treatment-experienced pediatric subjects. Of note, one subject had no previous use of ARVs. In addition, 4 subjects had no history of HAART regimen (i.e. had history of exposure to only 1 class of ARV. This may reflect use of ARV to prevent maternal to child transmission of HIV).

One of the primary efficacy endpoint for this trial was plasma viral load < 50 copies/mL at Week 24. Raltegravir adult tablets and chewable tablets, in combination with OBT, demonstrated good antiviral activity over the 24 week trial period. The proportion of subjects with plasma viral load < 50 copies/mL at Week 24 (based on FDA snapshot algorithm) was 53% (51/96). In addition, 66% (65/96) of subjects achieved an HIV RNA level < 400 copies/mL by Week 24 (Table 2). The observed success rate (HIV RNA <50 copies/mL) in this pediatric trial is generally comparable to the efficacy demonstrated in the treatment experienced adult trials (BNCHMRK 1 and 2) where raltegravir with OBT versus OBT alone in subjects with documented resistance to at least one drug class (NNRTIs, NRTIs, PIs) was evaluated. The proportion of subjects with HIV RNA < 50 copies/mL at 24 and 96 weeks were 63% and 55%, respectively, in the raltegravir plus OBT arm.

Table 2 Virologic outcome at Week 24 based on snapshot algorithm

Virologic Success n, (%)	**HIV RNA < 50 copies/mL**: 51/96 (53.1%)	**HIV RNA < 400 copies/mL**: 63/96 (65.6%)
Virologic Failures n, (%)	**HIV RNA ≥ 50 copies/mL**: 44/96 (45.8%)	**HIV RNA ≥ 400 copies/mL**: 32/96 (33.3%)
Ongoing and viral load >50 copies/mL	42/44(95%)	28/32(88%)
Discontinued due to virologic failure	0	
Discontinued due other reasons and viral load >50 copies/mL at time of the discontinuation	2/44(5%)	4/32(13%)
Switch in background regimen not allowed by protocol	0	0
No Virologic Data at 24 Week Window		
Discontinued trial/trial drug due to AE or death	0	0
Discontinued trial/trial drug for Other Reasons	0	0
Missing data during window but on study	1/96 (1%)	1/96 (1%)

Resistance

Refer to Dr. Sung Rhee, Microbiology Reviewer, for full details. Among the 44 subjects (46%) considered 'non-responders' according to the snapshot algorithm, 95% (42/44), were ongoing and had HIV RNA >50 copies/mL at Week 24, 2 subjects discontinued for 'other reasons' but their HIV RNA was >50 copies/mL at the time of the discontinuation, and 1 subject had 'missing data' during the Week 24 window. No subject was discontinued due to 'virologic failure'. Subjects who met the protocol-defined virologic failure (i.e. a confirmed decrease from baseline plasma HIV RNA of <1.0 log10 and HIV RNA >400 copies/mL at Week 24 or later; OR, virologic rebound at Week 24 or later) were evaluated for resistance. Resistance testing was done if subjects had HIV RNA >1000 and discontinued at Week 24 or later. Among the raltegravir treatment failure subjects (i.e. per protocol definition), 31 subjects had genotypic data available. Of the 31 subjects whose genotypic and phenotypic data were analyzed, HIV-1 variants harboring at least one of the 3 primary RAL resistance-associated (RAL^R) substitutions Y143C/H/R, Q148H/K/R, or N155H in the integrase protein were detected in 13/31 (42%) of subjects' on-treatment isolates; 7 of these (30%) were in the Final Dose population. As observed previously in the HIV-1-infected adult population (BENCHMRK and STARTMRK trials), substitutions mostly emerged independently as separate pathways to RAL resistance in the treatment failures (10/13, or 77%). Q148H/R was most frequently observed (9/13, or 69% of isolates. The secondary RAL substitutions were detectable in most of those isolates with emerging primary RAL substitutions (10/13, or 77%).

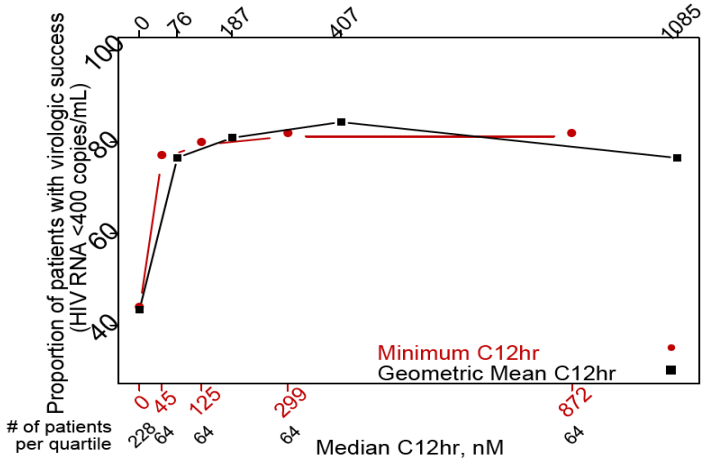
In addition, genotypic resistance analysis of the pooled data (adults and pediatrics) showed that HIV IN Q95K/R substitution was found exclusively in the same virus population harboring the primary RAL resistance-associated substitution. Thus, a recommendation has been made by the microbiology reviewer that Q95K/R be included in the list of the secondary RAL resistance-associated substitutions that may contribute to RAL resistance in the presence of the primary RAL resistance-associated substitutions. This recommendation has been negotiated and accepted by the Applicant.

Subgroup and Exposure-response Analysis

Similar to adults, in children, there does not appear to be any difference in virologic response based on the following subgroup analysis: age, race, baseline HIV RNA category, and baseline CD4 cell count category.

In adult subjects, 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).

Figure 3 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} quartiles. A similar trend was observed with subjects achieving HIV RNA <50 copies/mL (not shown)



Source: Clinical Pharmacology Review

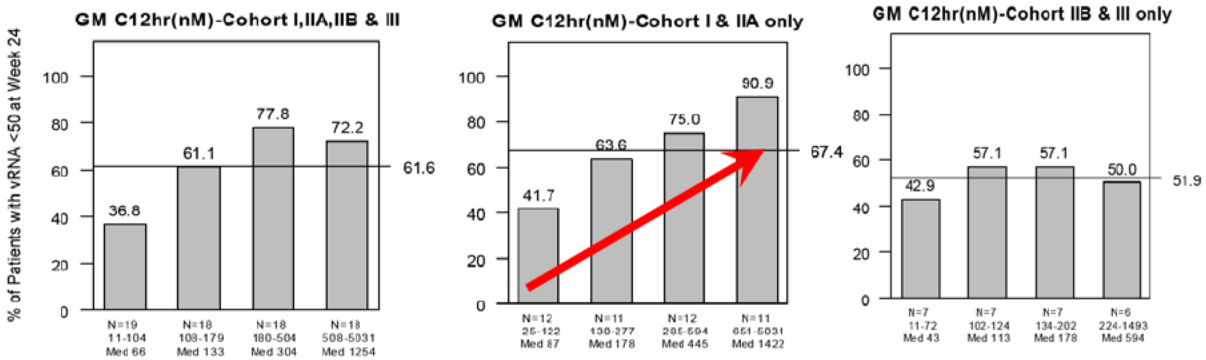
However, two PK/PD relationships appeared to exist in these pediatric subjects: 1) apparent lower response rate with the film-coated formulation (primarily driven by cohort 1), and 2) apparent gender difference in response rate (primarily driven by cohort 1). In both cases, it appears that adherence is the likely reason for the discrepancies.

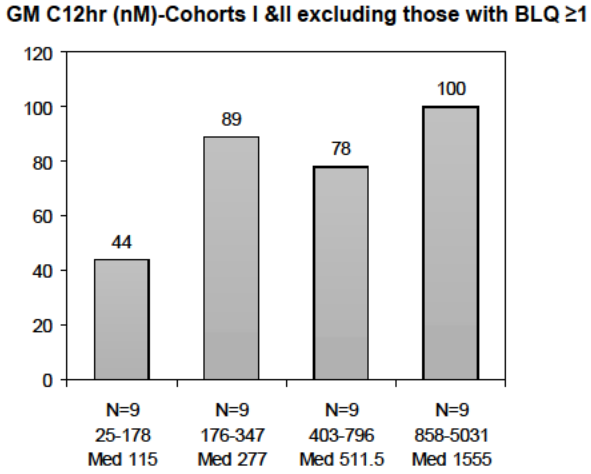
Formulation Logistic regression analysis was conducted using *sparse* PK data to explore potential associations between raltegravir PK exposures and antiretroviral responses. Exposure-response analysis based on formulation suggested a statistically significant association between raltegravir concentrations (C_{all}, GM C_{12}) and composite virologic success at Week 24 across all cohorts (Figure 4a). This was evident only for Cohorts 1 and 2a (film-coated tablets). As there were only 4 subjects in Cohort 2a in the final PK/PD analysis, the finding is largely driven by Cohort 1 (Figure 4b). Suspecting medication non-compliance as a possible cause for the exposure-response association, the Applicant repeated the exposure-response analysis by excluding subjects with ≥2 plasma samples with drug concentration below level of quantification (BLQ) across all cohorts. Similarly, 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 BLQ samples. When excluding subjects with ≥1 BLOQ samples from the analysis, the exposure-response association largely disappeared (Figure 4d), except for the lowest quartile, where individuals with GM C_{12} concentrations ≤178, had the lowest virologic success rates. Of note, the median C_{12} 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). In addition, it should be noted that the GM C_{12} concentrations within the lowest quartile remained above the protocol defined minimum trough of > 33nM.

Finally, The Applicant also tested for development of viral resistance to raltegravir in blood samples obtained from subjects in the final dose population who failed to achieve ≥1 log drop or HIV RNA<400 copies/mL at Week 24. Of the subjects who met the endpoint of ≥1 log drop or HIV RNA<400 copies/mL at Week 24 *and* who had resistance testing done, none of the subjects with BLQ values had raltegravir-associated resistance mutations.

Figure 4a-d GM trough and virologic response





Source: Dr. Ruben Ayala, Clinical Pharmacology Reviewer

Gender As mentioned previously, data from the intensive PK part of the trial (stage 1) showed that the exposures (AUC and C_{12}) were similar between the genders. Despite this observation in stage 1, the proportion of females with HIV RNA <400 copies/mL at Week 24 was 61%,

compared to 83% for males; the proportion of female subjects with HIV RNA < 50 copies/mL at Week 24 was 43% compared to 66% for males. Although an interesting finding, given the trial design (open labeled and single arm) and the small number of subjects, one should be cautious when interpreting this finding. The gender discordance was primarily driven by Cohort 1, adolescent subjects. It appears this was likely due to higher incidence of non-adherence in the female subjects as evident by higher incidence of drug concentration below level of quantification (BLQ) scores in females: the distribution of the mean *sparse PK* C_{all} and GM C_{12} were similar between the genders, though there appears to be a higher incidence of outlier with low values for females compared to males, particularly in Cohort 1. These low outlier values represent subjects with concentration values that were below the assay limit of quantification (BLQ). In summary, based on the findings from the adult trials (which enrolled larger numbers and were controlled trials) there is no difference between virologic responses and raltegravir exposures based on gender. Therefore, it reasonable to believe the finding in the adolescent subjects is likely driven by poor adherence and exposure.

7. Safety Evaluation

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 on 96 pediatric subjects who received the to-be-marketed dose (final dose, FD) for at least 24 weeks. Of note, subset of subjects (i.e. those age 6 to 18 years of age) had safety data for up to 48 Week. Because enrollment was sequential (i.e. oldest pediatric subjects- Cohort 1, were enrolled first and the youngest subjects- Cohort 3, were enrolled last), the younger subjects did not have 48 Week data at the time of the data cut-off. Raltegravir, in combination with other antiretroviral drugs, was generally safe and tolerated in pediatric subjects 2 to 18 years of age. No new safety signals were identified. In general, the adverse events (AEs) reported were similar to those reported in adults.

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. Vargas-Kasambira's review for additional details.

With the administration of the final dose (FD) in the 24 week treatment period, clinical adverse events were common (80%), while serious adverse events occurred with less frequency (13%). Significant numbers of the adverse events were related to underlying HIV-related disease conditions and common childhood illnesses. Clinically significant laboratory events were also infrequent. There were no discontinuations over 24 weeks of treatment due to clinical adverse events or laboratory toxicities. There were no deaths reported during the 24 week treatment period. In general, the nature of adverse events reported in this pediatric trial was similar to that of adult subjects reported during clinical trials.

Because the safety from Week 48 is incomplete (i.e. complete only for Cohort 1 and 2), the discussions below are focused on the Week 24 data for the final dose population. Additional safety reviews will be conducted in the future once the study is completed and the Applicant submits the full 48 week data. Based on the currently available, partial 48 week data, the frequency, types, severity and seriousness of adverse events during the 48 week treatment period remained generally similar to the 24 week results. There were no discontinuations due to clinical or laboratory events and no new *treatment-related* grade 3 or above events were

reported. One death was reported at Week 29, a 15 year old female who died of severe respiratory distress due to pneumonia. The cause of death is unlikely to be related to study drug, as the subject had multiple co-morbidities (CD4 1%, HIV RNA >100,000 copies/mL).

At the Week 24 time cut-off, the most common adverse events (all grades, regardless of causality) reported with ≥ 10% incidence (by preferred terms) are: cough (32%, n=31), pyrexia (24%, n=23), vomiting (15%, n=14), diarrhea (13%, n=12), nasal congestion (13%, n=12), and oropharyngeal pain (13%, n=12).

By Week 24, Grade 3 or higher adverse events (regardless causality) reported with >1% incidence include (by preferred term): pneumonia (3%), pyrexia (2%), gastroenteritis (2%), and suicidal behavior (2%) [see discussion below for psychiatric events]. One subject had *treatment-related* grade 3 adverse events reported. Subject was a 12 year old male, enrolled in Cohort 1 who had no prior history of psychiatric disorders. The events included abnormal behavior, psychomotor hyperactivity and insomnia.

Among the adverse events of special interest identified for raltegravir are rash, psychiatric and hepatic events. Because of the interest in these events, both 24 and 48 week events were evaluated and events (i.e. up to Week 48) are summarized below:

Rash, reported with the final dose population during the 24 week treatment period include allergic dermatitis (4%), rash (4%), generalized rash (2%), macular rash (2%) and papular rash (1%); events in the 48 week treatment period include rash (9%), allergic dermatitis (6%), generalized rash (5%), drug eruption (2%), macular rash (2%) and papular rash (1%). Because concomitant medications included NRTIs (e.g. abacavir) and/or NNRTIs which are known to cause rash, it is difficult to conclude that the events were treatment (raltegravir) related. One subject had serious (Grade 2) event of allergic dermatitis on Day 17 of treatment (concomitant drugs included efavirenz, abacavir and bactrim; there was no associated fever or mucous membrane involvement). This subject was hospitalized with temporary interruption of raltegravir. With exception of one subject who had Grade 3 generalized rash, no other rash was reported as severe. Finally, there was no report of hypersensitivity and no subject discontinued treatment permanently due to rash.

Psychiatric disorders were examined in detail in this pediatric population because of postmarketing reports as well as reports in the literature, regarding adult patients with depression and suicidal behaviors. By Week 48 of the study, 10% of final dose population reported psychiatric disorders (regardless of causality, severity): depression (3%), suicidal behavior (2%), abnormal behavior (2%), adjustment disorder (1%), anger (1%), attention deficit/hyperactivity disorder (1%), insomnia (1%), mood swings (1%), restlessness (1%), and sleep terror (1%). Of note, 17% of the final dose population had previous history of psychiatric disorder and 9% had history of neuropsychiatric therapies.

By Week 24, two subjects had Grade 3 events: a 12 year old male with abnormal behavior, psychomotor hyperactivity and insomnia; and an 18 year old male who gestured suicide by swallowing 6 diphenhydramine capsules (this event was also considered serious). Furthermore, by Week 24, two subjects had serious psychiatric events- suicidal behaviors. One of the subjects is the 18 year-old mentioned above who swallowed diphenhydramine capsule after an argument with his mother. He had no previous history of suicidal ideation, gesture or attempt. The second subject, a 15 year old female, with history of behavioral issues, placed a rope/cord around her neck and gestured suicide

after an argument with grandmother. Neither was admitted to a hospital for psychiatric care. Additional psychiatric events related to suicide or depression after Week 24 include: one subject with no prior history of depression reported with Grade 3 or higher event of major depression and depression and was admitted to inpatient psychiatric unit. Subject's father had died at the time of the depression; another subject was reported to have bipolar disorder (subject had extensive history of psychiatric disorders).

In summary, with the exception of the subject with suffered from abnormal behavior, psychomotor hyperactivity and insomnia, the events reported for the other subjects could not be said to be definitively related to study drug as the events occurred in concurrent with other factors (e.g. family arguments, deaths) or subjects had previous history of mental illness. The proposed labeling will reflect abnormal behavior, psychomotor hyperactivity and insomnia. But in addition, once the full 48 week data is submitted (in addition to any post-marketing psychiatric events), the Division will reevaluate what, if any, additional language should be included in the label.

Hepatic-related events were considered submission specific primary safety concerns. One subject, developed Grade 4 elevation in ALT and AST and event was thought to be possibly related to raltegravir or part of an inflammatory process (at the time of the elevation, subject also had pneumonia and splenomegaly). Refer to laboratory section below for liver-related laboratory toxicities.

Grade 3 or higher laboratory events during the 24-week treatment period included increase in ALT (n=1), AST (n=1), bilirubin (n=3), creatinine (n=1) and decrease in neutrophil count (n=8). None of the subjects with elevated bilirubin had concurrent elevation in ALT, AST and/or alkaline phosphorus. With exception of the subject with elevated ALT and AST, none of the events were considered drug related; no subject discontinued due study drug due to laboratory toxicities.

In summary, raltegravir when co-administered other ARTs, was generally safe and tolerated. There were no treatment-related deaths or discontinuation from study due to adverse events. There were no subjects who met the definition of hy's law and no case of hypersensitivity was reported. The psychiatric events of depression, suicidal ideation or attempt have been previously reported in the adult patient population (post-marketing). Additional safety review will be conducted once the full 48 Week data is submitted.

8. Labeling

Package Insert

The following revisions to the Dosing and Administrations section of the USPI were successfully negotiated:

(b) (4)

Patient Package Insert

After routine consultation to the Division of Risk Management (DRISK) was made, significant updates to the PPI were recommended. The primary content of the recommendations are formatting and reorganization of the information contained within the PPI. In addition, new information related to the chewable tablets (including information about PKU) has been included in the PPI. These recommendations have been incorporated into the label.

9. Outstanding Issues

None

10. Recommendations/ Risk Benefit Assessment

I recommend the approval of this pediatric application. The data from the current NDA and sNDA 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 2 to 18 years of age. The final dose selected and administered let to mean AUC exposures that were comparable to the targeted adult mean AUC.

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 53% and 66%, respectively. No subject discontinued due to protocol defined virologic failure or adverse events.

There were neither new safety signals identified nor were there major safety differences identified between pediatric subjects and adults.

Recommendation for other Postmarketing Requirements and Commitments

The following are PREA postmarketing requirements

1846-1 Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from ages 0 to <4 weeks of age. The study will determine the safety, antiviral activity and pharmacokinetic profile of raltegravir in neonates. The antiviral activity will be based on the results of virologic response over at least 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks.

Final Protocol Submission:	December 2012
Study/Trial Completion:	April 2014
Final Report Submission:	January 2015

582-3 Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 4 weeks to 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.

Final Protocol Submission:	Submitted September 2008
Final Report Submission:	June 2011

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
12/19/2011