CLINICAL REVIEW

Application Type	**NDA/sNDA**
Application Number(s)	**NDA 203045/NDA 22145**
Priority or Standard	**P**
Submit Date(s)	**June 30, 2011**
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Division / Office	**DAVP/OAP**
Reviewer Name(s)	**Tafadzwa Vargas-Kasambira, M.D., M.P.H.**
Review Completion Date	**November 21, 2011**
Established Name	**Raltegravir potassium**
(Proposed) Trade Name	**ISENTRESS®**
Therapeutic Class	**Antiretroviral drug**
Applicant	**Merck Research Laboratories**
Formulation(s)	**Film coated tablets (400 mg)** **Oral chewable tablets (25 mg and 100 mg)**
Dosing Regimen	**Raltegravir 400 mg film coated tablets twice a day (adolescents aged 12 to 18 years, and children 6 to 12 years weighing ≥ 25 kg), and raltegravir oral chewable tablets 6 mg/kg twice**

	a day to maximum 300 mg twice a day (children aged 2 to < 12 years)
Indication(s)	**Treatment of HIV-1 infection**
Intended Population(s)	**Pediatric patients aged 2 to 18 years**

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 203045 and supplement to NDA 22-145 (submission number 22) containing interim data from the pediatric clinical trial IMPAACT P1066/Merck 022 supports the indication for use of Isentress® (raltegravir potassium) in combination with other antiretroviral drugs for the treatment of HIV-1 infection in pediatric patients 2 years of age and older. This reviewer recommends the approval of the NDA and supplemental NDA (sNDA), submission number 22. Raltegravir, in combination with other antiretroviral drugs, resulted in reduction in HIV-1 RNA viral load and increases in CD4 cell counts over the 24 week study period across all ages studied.

Through the review of this NDA and sNDA, no deficiencies that would preclude the approval of this submission were identified. Raltegravir potassium (raltegravir) was studied in a single Phase I/II, open-label, non-comparative trial in which 126 pediatric subjects were enrolled and 96 of which received the to-be-marketed dose. The trial design comprised of two stages: Stage I was a dose-finding stage which also evaluated the short term safety and efficacy of raltegravir in a limited number of subjects; Stage II evaluated the safety and efficacy of the final selected dose, for a minimum of a 24-week treatment period. Pediatric subjects were stratified into cohorts by age (≥ 12 to < 19 years; ≥ 6 to < 12 years; and ≥ 2 to < 6 years). The oldest subjects (≥ 12 to < 19 years) and subjects ≥ 6 to < 12 years weighing at least 25 kg received the marketed, adult raltegravir film-coated tablet formulation; the younger subjects (≥ 2 to < 6 years) and other subjects ≥ 6 to < 12 years received a new oral chewable tablet formulation. Subjects ≥ 4 weeks to < 2 years of age received a new formulation of oral raltegravir granules for suspension in water, and study in this age group is currently ongoing.

Raltegravir exposures in pediatric subjects approximated that in adult subjects, with the geometric mean (GM) AUC values falling in the pre-specified target AUC range of 14 to 25 μM*hr. All GM C_{12hr} values in the pediatric subjects exceeded the pre-specified target of > 33 nM. Therefore, the proposed raltegravir doses for pediatric patients appear to be acceptable.

Pediatric subjects enrolled in the trial were treatment-experienced, as evidenced by baseline PSS score (22% had a PSS of 0-1) and history of previous ARV experience (67% had previously used at least 3 classes of ARVs). Overall, 53% of subjects enrolled in the trial had HIV RNA < 50 copies/mL at Week 24, and 66% achieved HIV RNA level < 400 copies/mL at Week 24. A virologic success rate of 53% is not unusual in such a treatment-experienced population. In the adult, treatment-experienced trial, 46% of the subjects in the raltegravir arm had PSS score 0-1; the virologic success rate (HIV RNA < 50 copies/mL) at Week 24 was approximately 63 percent.

Additional efficacy analyses were conducted for this pediatric trial, including subgroup analyses by age, gender and tablet formulation. The numbers of subjects enrolled in each cohort in the

Final Dose population varied significantly, with the oldest subjects (Cohort I) having the highest number of enrollees (N=59). Despite differences in numbers of subjects enrolled in each cohort or age group, there were no significant differences in response rate between the cohorts: the proportion of subjects with HIV RNA < 50 copies/mL at Week 24 ranged from 56% in the oldest subjects, to 50% in the youngest. The age range of pediatric subjects in the trial was a proxy for raltegravir formulation (older subjects received marketed adult tablet, younger subjects received the chewable tablet), and the virologic response suggests that formulation difference did not affect efficacy. Additional subgroup analysis did not reveal any significant differences in efficacy, except for gender, in which males had a 24% higher virologic response rate (HIV RNA < 50 copies/mL) than females at Week 24. This difference was primarily driven by Cohort 1. The most likely reason for the discrepancy appears to be adherence - female subjects had poorer adherence compared to males, as evidenced by the pharmacokinetic and adherence data. Given the small sample size of the trial, and the unrevealing results of the ad hoc analyses performed to explore this discrepancy, it is unlikely that the virologic outcomes were driven by inherent difference in raltegravir exposures between male and female adolescents. More importantly, no gender difference was noted during the adult clinical trial where larger numbers of subjects were enrolled and the trials were blinded with comparators.

The applicant demonstrated an acceptable safety profile for raltegravir in combination with other antiretroviral drugs. Adverse events in this pediatric population were common (80%), while serious adverse events were fairly uncommon (13%), and none required discontinuation of trial drug over from Week 0 to Week 48 of the trial period. A substantial number of adverse events were due to underlying disease conditions and common childhood illness. Clinically significant laboratory events were infrequent, and did not lead to trial drug discontinuation. The nature of adverse events in these pediatric subjects was similar to that of adult subjects noted previously.

This reviewer recommends the approval of the marketed raltegravir film-coated (400 mg tablet) for use in HIV-1 infected children 6 years of age and older (if weight is at least 25 kg), and the approval of the new chewable raltegravir oral tablet for children 2 years of age and older and weighing at least 10 kg. The chewable tablet formulation should be weight-based (approximately 6 mg/kg twice a day). The option of the use of either the marketed adult tablet or the chewable tablet is beneficial for children 6 to < 12 years of age who may or may not be able to swallow tablets.

Similar to other pediatric trials which evaluate safety and effectiveness of ARVs, this trial was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe the findings.

1.2 Risk Benefit Assessment

Raltegravir is the only integrase strand transfer inhibitor that is currently approved for marketing (in adults), and given the relatively limited HIV treatment options that are available for pediatric patients, raltegravir would provide a much-needed alternative for such patients. Virologic response has been demonstrated in this pediatric trial using both formulations of raltegravir (i.e.

the marketed adult tablet and the new chewable tablet) in combination with other antiretroviral drugs over a 24-week treatment period, and there is evidence of durability to at least 48 weeks. Efficacy was consistent across age groups and in various subgroups, although a greater virologic response was found in males compared with females. This discrepancy is not thought to be clinically significant given the confounding aspect of probably non-adherence in female subjects in the trial. Immunologic success was also demonstrated in this trial, with a substantial increase in CD4 count and percent over the 24- and 48-week treatment periods, across age groups and formulation types.

Emergence of raltegravir resistance monitoring was done on subjects who met the protocol-defined measure of virologic failure (i.e. a confirmed decrease from baseline plasma HIV RNA of <1.0 $\log_{10}$ and HIV RNA >400 copies/mL at Week 24 or later; OR, virologic rebound at Week 24 or later). Resistance testing was done if subjects had HIV RNA >1000 and discontinued at Week 24 or later. Among the raltegravir treatment failure subjects (as defined above), 31 subjects had any genotypic data available; 13/31(42%) of these raltegravir treatment failure pediatric subjects developed HIV-1 variants harboring at least one of the three primary raltegravir resistance-associated substitutions (Y143C/H/R, Q148H/K/R, and N155H substitutions within the HIV-1 integrase protein), which is consistent with observations in adults.

Raltegravir was, overall, generally safe and tolerable in pediatric subjects in this trial. There was a single death that occurred due to the subject's underlying disease condition and not likely due to the trial drug. Many subjects experienced adverse events, though a much lower proportion experienced serious adverse events, or Grade 3 or 4 clinical or laboratory events. No adverse events led to trial drug discontinuation. Adverse events of special interest with the use of antiretroviral agents such as raltegravir (metabolic disorders, IRIS, rash, AST/ALT elevations, psychiatric disorders, and AIDS-defining conditions) occurred with low frequency, and no new safety signals, as compared with the adult raltegravir safety profile, were identified.

Use of raltegravir, as with all antiretroviral drugs, is not without risk. The observed risks of raltegravir use have been described previously, and the rate and nature of the adverse events were similar to those in adults. The Safety Update Report on the use of raltegravir in pediatric patients worldwide has revealed few reports of adverse events, and none of them has been classified as serious. Of note, the size of the safety database for this recently approved antiretroviral drug is limited in size for pediatrics, and particularly so for children less than 2 years of age. The trial will continue to follow subjects for a total of 5 years of treatment, and will provide additional follow-up safety data. Also important to note is that a post-marketing monitoring plan was set in place by the applicant following approval of raltegravir for use in adults, and this Risk Management Plan (RMP) has been updated with safety information for the pediatric population in this trial.

This reviewer supports approval of raltegravir for HIV-1 infected pediatric patients 2 years of age and older weighing at least 10 kg. The applicant has provided an adequate amount of data to demonstrate that raltegravir is safe for use in the pediatric population as per the proposed indication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Postmarket Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will submit periodic safety reports for review.

1.4 Recommendations for Postmarket Requirements and Commitments

The current submission partially fulfills the Pediatric Written Request, and no additional pediatric post marketing study commitments will be sought. The current submission also fulfills one of the Post Marketing Commitments (see Section 2.5). A trial in HIV-1 infected children ≥ 4 weeks to < 2 years of age is currently ongoing, and the protocol for a trial in pediatric subjects < 4 weeks of age is in the planning stages.

2 Introduction and Regulatory Background

2.1 Product Information

- Established Name: Raltegravir potassium
- Trade Name: ISENTRESS®
- Description: White to off-white powder. (b) (4) and additional constituents
- Chemical Name: *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt
- Empirical Formula: $C_{20}H_{20}FKN_6O_5$
- Pharmacological Class: HIV integrase strand transfer inhibitor
- Proposed Indication and Dosing: Treatment of HIV-1 infection in pediatric patients aged 2 to 18 years

  Children and Adolescents
  - 12 years of age and older: One 400 mg tablet twice daily, orally
  - 6 through 11 years of age (2 dosing options):
    - One 400 mg tablet twice daily, orally (if at least 25 kg in weight) **OR**
    - Chewable tablets: weight based to maximum dose 300 mg twice daily
  - 2 through 5 years of age:
    - Chewable tablets: weight based to maximum dose 300 mg twice daily

Table 1. Recommended Dose for ISENTRESS Chewable Tablets in Pediatric Patients 2 to through 11 Years of Age

Body Weight (kg)	Body Weight (lbs)	Dose	Number of Chewable Tablets per dose (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.

- Dosage Form: 400 mg
  100 mg scored and 25 mg

2.2 Tables of Currently Available Treatments for Proposed Indications

The current indication is for the treatment of HIV-1 infection in children, in combination with other antiretroviral drugs. As of October 2011, a total of 18 drugs had been approved for this indication in the United States. The currently approved drugs for this indication are described specifically in Table 2:

Table 2. Currently Available Treatments for Treatment of HIV-1 Infection in Children

Brand Name	Generic Name	Pediatric Age with Use Labeling
NRTI		
Combivir®	lamivudine and zidovudine	>12 yr
Emtriva®	Emtricitabine, FTC,	≥ 0-3 months old
Epivir®	lamivudine, 3TC	≥3 months old
Retrovir®	zidovudine, AZT, ZDV	≥ 4 weeks old
Truvada®	tenofovir disoproxil/emtricitabine	≥ 12 years old
Videx EC®	enteric coated didanosine	
Videx®	didanosine, ddI,	≥ 2 weeks old
Viread®	tenofovir disoproxil fumarate, TDF	≥ 12 years old
Zerit®	stavudine, d4T	≥ Birth
Ziagen®	abacavir	≥ 3 months old
NNRTI		
Sustiva®	Efavirenz, EFV	>3 years old
Viramune®	Nevirapine, NVP	≥ 14 days old

Brand Name	Generic Name	Pediatric Age with Use Labeling
PI		
Aptivus®	Tipranavir	≥ 2 years old
Kaletra®	lopinavir and ritonavir	≥ 4 weeks old
Lexiva®	Fosamprenavir Calcium	≥ 2 years old
Norvir®	ritonavir	>1 month old
Prezista®	Darunavir, DRV	≥ 6 years old
Reyataz®	atazanavir sulfate, ATV	≥ 6 years old
Viracept®	nelfinavir mesylate, NFV	≥ 2 years old
Fusion Inhibitor		
Fuzeon®	enfuvirtide, T-20	≥ 6 years old
Entry Inhibitor		
Selzentry®	maraviroc	≥ 16 years old
Integrase strand transfer Inhibitor		
Isentress®	Raltegravir, RAL	≥ 16 years old

2.3 Availability of Proposed Active Ingredient in the United States

Raltegravir potassium, the active ingredient in Isentress, is available in the United States by prescription only. The proposed API for the treatment of HIV-1 infected pediatric subjects will be the same as the approved raltegravir. Pediatric subjects who are aged 12 years and older will access the same 400 mg film-coated tablet that is currently on the market. Those who are aged 6 through < 12 years will have two dosing options: the currently marketed 400 mg film-coated tablet if at least 25 kg in weight, or the new formulation of raltegravir chewable tablets (25 mg and 100 mg). Subjects 2 to < 6 years of age will be able to access the chewable tablets. It is not anticipated that there will be any difficulty accessing the proposed pediatric formulation.

2.4 Important Safety Issues With Consideration to Related Drugs

Pertinent safety issues applicable to HIV integrase inhibitors include clinical and laboratory adverse events such as metabolic disorders (dyslipidemias), immune reconstitution syndrome (IRIS), rash, AST/ALT elevations, psychiatric disorders (suicidal ideation and depression), and AIDS-defining conditions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

ISENTRESS® (raltegravir potassium) received accelerated approval for the management of HIV-1 infected treatment-experienced adults on October 12, 2007, based on the finding of virologic suppression in a patient population with few remaining treatment options.

The applicant submitted the first in-man trial of raltegravir (then known as L-900612) to the FDA under IND 69,928/S-000 on June 1, 2004. A meeting was held on June 29, 2005 between the applicant and DAVP at which Merck presented updated blinded safety and efficacy summary data from the two ongoing Phase 2 clinical trials, Protocols 004 and 005. On December 5, 2005 an End-of-Phase 2 meeting was held between the applicant and DAVP to discuss the available safety and efficacy data from the completed/ongoing Phase 1-2 clinical trials and the proposed plan to initiate Phase 3 clinical trials in adult subjects. Merck provided a summary of the dose-confirmation interim analysis from the Phase 2 trials (Protocols 004 and 005) to support Phase 3 dose selection. Based on the analysis of the Phase 2 data, the 400 mg BID was selected to carry forward to the Phase 3 trials.

DAVP granted Rolling Review designation on January 20, 2006 and in addition, DAVP agreed that the NDA would be filed with 16-week Phase 3 data, but would also include 24 week analyses as this would be used for labeling. The new primary endpoint for the Phase 3 trials (Protocols 018 and 019) would be HIV-1 RNA <400 copies/mL at Week 16. The Applicant agreed to include information on 48 week "all cause mortality" in the Phase 3, 48 week Clinical Study Reports.

During a pre-NDA teleconference held on December 1, 2006, DAVP requested reevaluation of the pediatric development program, given the significant virologic response to raltegravir in the 24-week data submitted from the Phase 2 trials and the need to determine safety in this population. DAVP recommended that a pharmacokinetic trial in children/adolescents be performed as soon as possible to support use of raltegravir in the pediatric population.

The applicant was informed in the initial approval letter that trials in pediatric subjects from birth up to 4 weeks of age (neonates) would not be requested under the Pediatric Research Equity Act (PREA) because there are too few pediatric subjects to study with the disease in this age group. However, the applicant is interested and planning to conduct a pediatric study in this age group. Therefore, a new PMR will be issued with the approval action of the current NDA/sNDA.

The approval letter also stated that trials in pediatric subjects from 4 weeks to 18 years would be deferred until June 30, 2011. These trials were considered postmarketing commitments (PMC) under Section 2 of the Pediatric Research Equity Act (PREA). Two PMCs were agreed upon during a teleconference held with the sponsor on October 5, 2007:

> 2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 to 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.
Protocol Submission Date: Ongoing
Final Study Report Submission Date: June 30, 2011

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.
Protocol Submission Date: September 30, 2008
Final Study Report Submission Date: June 30, 2011

In addition to PREA requirements, a Pediatric Written Request (PWR) was issued on August 18, 2006; this required the trial to be conducted in pediatric subjects (treatment-naïve or treatment–experienced) from birth to 18 years of age. The PWR was amended on June 27, 2007 to change the due date of the trial(s) from June 30, 2011 to January 5, 2015.

IMPAACT P1066, or P1066, was sponsored by The National Institute of Allergy and Infectious Diseases (NIAID) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and conducted by The International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group. Pharmaceutical support was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The study was coordinated and monitored by a core team consisting of members representing NIAID, NICHD, IMPAACT, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. The IND sponsor is the Division of AIDS (DAIDS); all clinical sites conducted the study under this IND and in accordance with DAIDS policies and standard operation procedures (SOPs), as outlined in the protocol registration manual from the DAIDS Office for Policy in Clinical Research Operations (OPCRO).

The sponsor submitted data aimed at fulfilling PMC #2 on June 30, 2011. A waiver request was submitted to the Agency on September 12, 2011 for pediatric subjects 12 to 18 years of age for use of raltegravir chewable tablets. The rationale behind the request was that raltegravir has been studied in HIV-infected subjects 12 to 18 years of age using the adult tablet formulation in IMPAACT Trial P1066, and that adequate PK, safety and efficacy have been demonstrated in this age group. In addition, the adult tablet is an age-appropriate formulation in adolescents, and the chewable tablet formulation of raltegravir would not provide a meaningful therapeutic benefit over the adult tablet formulation.

A deferral request was also submitted on September 12, 2011, for pediatric subjects zero to 2 years of age for use of raltegravir chewable tablets. (b) (4)

The currently submitted pediatric trial fulfills the requirements stated under PREA and PWR. The applicant has submitted complete efficacy and safety data from Weeks 0 to 24, as well as the majority of such data up to Week 48.

Please refer to Appendix (Section 9.4) for review of the complete PWR and PREA.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate. A consult request was made to the Office of Scientific Investigations (OSI) for inspection of the Bioanalytical site at the (b) (4), in order to assess significant pharmacokinetic results pertinent to the decision on whether or not to grant approval.

The final inspection report was issued on November 23, 2011. The inspection was conducted on (b) (4), and a Form FDA 483 was issued, given the observation that there had been a failure to record the preparations of calibration standards used in 25 bioanalytical runs, and quality control samples used in three bioanalytical runs on the Daily Assay Worksheet for raltegravir analyses. A response to the Form FDA 483 had not been received from the inspected site at the time of issuance of the inspection report, but OSI noted that the observation was unlikely to affect the raltegravir assay results. The Division of Bioequivalence and GLP Compliance (DBGC) recommends that the data for the analytical portion of Trial IMPAACT P1066 may be acceptable for review.

3.2 Compliance with Good Clinical Practices

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Prior to the initiation (i.e., before screening or enrollment of the first subject) of a DAIDS funded and/or sponsored study/trial, all key clinical site personnel must have received training as described in the Requirements for Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training for Clinical Research Site Personnel policy; training was also received on a recurring basis as specified by this policy. Key personnel included individuals who are involved in the design and conduct of NIH-funded human subjects' clinical research.

3.3 Financial Disclosures

The sponsor submitted financial information pertinent to the application. The statement specified that the sponsor had not entered into any financial arrangement with particular clinical investigators (IND sponsor is the Division of AIDS (DAIDS), with pharmaceutical support provided by the sponsor Merck), whereby the value of compensation to the investigators could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)), had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues have been identified. Please see CMC review by Andrew Yu for further details. Briefly, CMC concluded that the NDA had provided sufficient information to assure identity, strength, purity, and quality of the drug product. Raltegravir Chewable tablets are provided in two strengths, 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 that allows dosing of 50 mg. The pediatric chewable tablets are not bioequivalent with the adult tablet.

4.2 Clinical Microbiology

Please see Clinical Microbiology Review by Dr. Sung Rhee for further details. Briefly, Monitoring for emergence of raltegravir resistance was done on subjects who met the protocol-defined criteria for 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). Resistance testing was conducted if subjects had HIV RNA >1000 and

discontinued at Week 24 or later. Among the raltegravir treatment failure subjects (as defined above), 31 subjects had any genotypic data available; 13/31 (42%) of the raltegravir treatment failure pediatric subjects developed HIV-1 variants harboring at least one of the three primary raltegravir resistance-associated substitutions (Y143C/H/R, Q148H/K/R, and N155H substitutions within the HIV-1 integrase protein). Most (12/13, or 92%) of these HIV-1 variants were less sensitive to raltegravir (5 to > 180-fold, compared to the subject's pre-treatment isolate and/or wild-type reference HIV-1). Secondary raltegravir resistance-associated substitutions were also detected in most (10/13, or 77%) of those isolates with emerging substitutions of this type. HIV-1 variants with the primary raltegravir resistance-associated substitutions emerged in a significantly greater proportion of the failures who did not receive the final selected dose of raltegravir (6/8 Final Dose subjects, or 75%), compared with those who did receive the final selected dose (7/23, or 30% of other subjects). Suboptimal dosing of raltegravir may contribute to the increased emergence rate of raltegravir resistant variants during treatment in some of the failures in the non-recommended dose population: 3 of the 6 subjects received raltegravir 200 or 300 mg BID (recommended dose for these 3 subjects is 400 mg BID).

Genotypic resistance analysis of pooled data from multiple trials of raltegravir (BENCHMRK, STARTMRK, SWITCHMRK, and P1066) revealed that HIV-1 in Q95K/R substitution was found exclusively in the same virus population harboring the primary raltegravir resistance-associated substitutions. Eleven raltegravir treatment failures were identified from 4 trials to develop HIV-1 variants harboring a substitution in Q95 (changed to H [n=1], K [n=3], N [n=2], and R [n=5]), which emerged while on raltegravir, and the primary raltegravir resistance-associated substitutions were detected in all 11 isolates. Q95K has been shown to enhance N155H-mediated raltegravir resistance and improve the impaired replication of the N155H mutant virus. It is therefore recommended that Q95K/R be included in the list of the secondary raltegravir resistance-associated substitutions that may contribute to raltegravir resistance in the presence of these primary substitutions. This recommendation has been included in the proposed label and is currently under negotiation with the Applicant.

4.3 Preclinical Pharmacology/Toxicology

Isentress is an FDA-approved drug. There were no new Pharmacology/Toxicology studies conducted or submitted with the current NDA/sNDA. Therefore, the Pharmacology/Toxicology team did not complete a review. Please refer to the original NDA review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Raltegravir is a potent and selective inhibitor of HIV-1 integrase catalyzed strand transfer. Integrase catalyzes the stepwise process that results in integration of the HIV-1 DNA into the genome of the host cell, a process that comprises assembly of integrase in a stable pre-integration complex with viral DNA, endonucleolytic processing of the viral DNA ends, and strand transfer or joining of the viral and cellular DNAs. Integrase nicks each strand of the host cell DNA and

exposes the 5' phosphate groups, enabling covalent bonding of host and viral DNA. After this strand transfer is complete, host cell enzymes repair gaps between the viral and host DNA. Raltegravir prevents or inhibit the binding of the pre-integration complex to host cell DNA, thus terminating the integration step of HIV replication.

4.4.2 Pharmacodynamics

Pharmacodynamic properties of raltegravir have been explored previously in clinical trials. Raltegravir demonstrated rapid antiviral activity in a monotherapy trial using raltegravir at a dose of 400 mg BID, with mean viral load reduction of 1.66 $\log_{10}$ copies/mL by Day 10. The antiviral response has been found to be similar among adult subjects taking higher doses.

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. ISENTRESS did not appear to prolong the QTc interval for 12 hours postdose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper Cl: 3.1 msec).

4.4.3 Pharmacokinetics

Please see Clinical Pharmacology review by Dr. Ruben Ayala for further details.

P1066 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 through 18 years of age. Raltegravir was administered with background antiretrovirals, and the regimen was optimized after sampling for PK evaluation. Raltegravir was administered orally as the adult tablet formulation or as a chewable tablet. A third formulation, oral granules for suspension in water, was available for subjects less than 2 years of age. (b) (4)

The stratification for subjects enrolled in this trial is as follows:

Cohort I: 12 to 18 years of age assigned to receive the adult tablet

Cohort IIA: 6 to less than 12 years of age assigned to receive the adult tablet

Cohort IIB: 6 to less than 12 years of age assigned to receive the chewable tablet

Cohort III: 2 to less than 6 years of age assigned to the receive chewable tablet

Pediatric dose selection for the three raltegravir formulations (adult tablet, chewable tablet, and oral granules) was conducted by approximating adult exposure at the 400 mg BID dose. This

dose was selected as it was the dose evaluated during the adult Phase 3 trials and later marketed for treatment of HIV-1 infection in adults.

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 OBT. Therefore, the goal of the pediatric dose selection was to target the adult exposure from the 400 mg BID, which is known to be an effective dose. In addition, doses were targeted to deliver trough values greater than the *in vitro* IC_{95} value (i.e. the inhibitory concentration).

In a Phase 2 dose-ranging trial, the mean raltegravir $AUC_{0\text{-}12hr}$ for each cohort in treatment-naïve HIV-1 infected adults was 14.3 µM*hr for raltegravir 400 mg BID monotherapy, and 25.3 µM*hr for raltegravir 400 mg BID in combination with tenofovir and lamivudine. In addition, the maximum $AUC_{0\text{-}12hr}$ was defined, for safety reasons, as < 45 µM*hr, which represents half the $AUC_{0\text{-}24hr}$ for 1600 mg given as a single dose in previous Phase I trials. The mean 95% IC_{95} *in vitro* for raltegravir is 33nM.

Subjects in Cohorts I (age 12 to 18 years) and IIA (age 6 to less than 12 and weighing at least 25 kg) received the adult tablet formulation of raltegravir. The initial PK target for Cohort I and IIA was to maintain a geometric mean (GM) raltegravir $AUC_{0\text{-}12hr}$ of greater than 14 µM*hr, with a simultaneous goal that the GM concentration at 12 hours post-dose (C_{12hr}) for the cohort be greater than 33nM, which, as noted previously, is the mean 95% IC_{95} *in vitro*.

The pharmacokinetic goal for subjects who received the chewable formulation differed slightly from those who received the tablet formulation because a biocomparison trial (Protocol 068) showed higher bioavailability of the chewable tablet when compared to the adult tablet. In order to limit the potential higher exposure with the chewable formulation, the target GM $AUC_{0\text{-}12hr}$ was refined to include an upper bound of a geometric mean of 25 µM*hr. The final target was therefore a GM $AUC_{0\text{-}12hr}$ between 14 and 25 µM*hr. The goal for the GM concentration at 12 hours post-dose (C_{12hr}) remained greater than 33nM.

Table 3 was prepared by Dr. Ruben Ayala of Clinical Pharmacology, and compares the pediatric exposures of raltegravir to that in adults. For dosing pediatric subjects, the applicant aimed for mean adult AUC values ranging from 14 to 25 µM*hr, as previously noted. In order to calculate the percent difference between adult and pediatric values, two methods were employed:

1) The percent difference between pediatric subjects and adults was calculated for both AUC bounds separately. More precisely, the difference between the adult lower bound AUC (i.e. 14 µM*hr) was compared to mean pediatric AUC values; similarly, the adult upper bound AUC (25 µM*hr) was compared to mean pediatric AUC values.

2) The mean AUC value between 14 and 25 μM*hr was 19.7 μM*hr, and this adult mean AUC value was compared to the pediatric mean AUC values.

Table 3. Comparison between Adult Raltegravir AUC values and Pediatric AUC Values

Cohort	Age range	Mean dose (mg/kg BID)	GM AUC_{0-12h} (μM*hr)	% relative to mean adult exposures
I	12 to ≤18y	390.9	15.7	-20.3
IIA	6 to ≤11y	400	15.8	-19.8
IIB	6 to ≤11y	230	22.6	14.7
III	2 to ≤5y	89.6	18	-8.6
Adults	≥19y	400	19.7	0

Source: Dr. Ruben Ayala, Clinical Pharmacology

Overall, 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_{12h} values exceeded the target of >33 nM. These results suggest 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.

5 Sources of Clinical Data

The submission contained data from a single Phase I/II open-label, non-comparative trial that was conducted in pediatric subjects in 56 centers (40 of which enrolled subjects) in five countries. Electronic materials submitted included the IMPAACT P1066 Clinical Study Report (CSR) for Week 24 and Week 48 data. Datasets for the trial were submitted as SAS transport files, and comprised demographic, safety and efficacy data. Case Report Forms (CRFs) for all subjects who died, for all subjects who withdrew from the trial due to related or unrelated adverse events, and for all subjects who experienced SAEs during trial drug dosing, were included. In addition, narratives were provided for all subjects who experienced deaths, SAEs (drug-related and non drug-related), and all drug-related AEs leading to withdrawal.

5.1 Tables of Studies/Clinical Trials

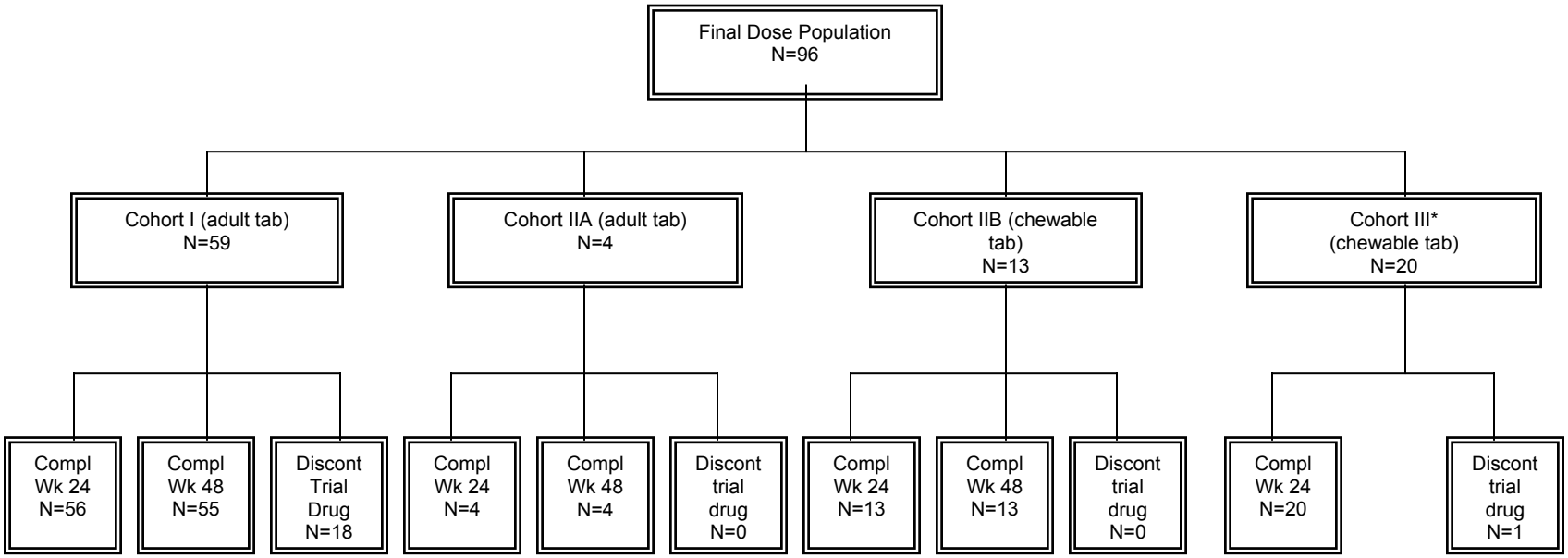
Table 4 summarizes the subject disposition of the clinical trial that was included in the submission.

Table 4. Clinical Trial Submitted in Support of NDA Application

Trial Name	Type of Trial	Number of Subjects Enrolled	Number of Subjects with ≥ 24 week data	Number of Subjects with ≥ 48 week data
P1066/022	Phase I/II open-label, non-comparative pediatric trial	126*	93	82

*Total of 126 subjects were All Treated population, while 96 subjects of these comprised Final Dose population

Figure 1. Disposition of Final Dose Population (as of February 14, 2011)



N = Number of subjects in each category (Note: subjects were enrolled in only one cohort. The same subject may be counted at Week 24 and Week 48, and may have discontinued by the data cut-off of February 14, 2011)
*Full Week 48 data for Cohort III were not available at the time of the clinical trial report

5.2 Review Strategy

IMPAACT Trial P1066 was reviewed for efficacy, safety and tolerability, and pharmacokinetics. The conclusions drawn by the applicant were independently corroborated through analyses conducted by the FDA. The primary endpoint and secondary endpoints in the trial were confirmed by this reviewer, who also evaluated trial design, subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results using JMP Statistical software.

Information from the Safety Update Report submitted by the applicant is also included in the safety section of this review.

Note that for all tables and figures that were not created by this reviewer, a footnote has been included to describe the source of the data. If the table or figure is created by this reviewer, no footnote is included.

5.3 Discussion of Individual Studies/Clinical Trials

IMPAACT Trial P1066/Merck 022 was the pivotal trial evaluating the use of raltegravir (both the marketed adult tablet and the new chewable tablet formulation) in pediatric subjects. The trial was submitted in support of the approval of raltegravir for treatment of HIV-1 in pediatric subjects 2 to < 18 years of age in combination with other antiretroviral agents.

IMPAACT P1066 is a phase 1/2, multicenter, open-label, non-comparative trial in pediatric subjects 4 weeks to < 19 years of age with documented HIV-1 infection and HIV RNA ≥ 1,000 copies/mL at screening. Safety, tolerability, PK parameters and efficacy of raltegravir in combination with OBT were evaluated over a 24-week and 48-week period.

Raltegravir was administered orally as the 400 mg adult tablet or as an ethylcellulose chewable tablet (2 through 18 years). (b) (4)

All subjects enrolled in the study were stratified into one of five age groups, in 6 cohorts:

Cohort I: 12 to less than 19 years of age assigned to receive the adult tablet

Cohort IIA: 6 to less than 12 years of age assigned to receive the adult tablet

Cohort IIB: 6 to less than 12 years of age assigned to receive the chewable tablet

Cohort III: 2 to less than 6 years of age assigned to the receive chewable tablet

Cohort IV: 6 months to less than 2 years assigned to receive oral granules for suspension

Cohort V: 4 weeks to less than 6 months assigned to receive oral granules for suspension

Subjects were enrolled into one of two sequential Stages: I and II. Stage I began with a dose-finding period which allowed dose selection by review of the PK and the short-term safety and tolerability of raltegravir in a limited number of subjects. After dose finding, Stage I subjects remained on trial in the Stage I extension.

Stage II was the chronic dosing period and enrolled additional subjects at the selected dose. Both Stage I subjects participating in the extension and Stage II subjects contributed data to the chronic dosing period, permitting the evaluation of longer term safety and antiretroviral activity in a larger number of patients.

All patients started an ARV OBT either after the intensive PK sampling was completed (Day 5 to 12 after beginning raltegravir for Stage I) or concurrently with initiation of raltegravir (for Stage II).

Complete data were available up to Week 24 (primary time point) for Cohorts I, IIA, IIB, and III; to Week 48 (secondary time point) for Cohorts I, IIA and IIB, and to Week 80 for Cohort I.

The primary objective was to evaluate the short-term safety and tolerability of raltegravir by adding the drug to a stable background therapy, and to evaluate the steady state plasma concentration profiles and PK parameters of raltegravir in pediatric subjects. The secondary objectives included evaluation of the safety and tolerability at the selected dose in combination with OBT in trial subjects, as assessed by review of the accumulated safety data over 48 weeks. The tertiary objective was to evaluate the long-term safety and efficacy of raltegravir in subjects treated for more than 48 weeks

Pharmacokinetic parameters characterized included Cmax, Cmin, Tmax, and AUC_{0-12}. For intensive PK evaluation of Stage I subjects in Cohorts I, IIA, IIB and III, blood samples were collected at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post dose. Population PK samples were collected for subjects in Stages I and II at Weeks 4, 8, 12, and 24. Subjects were followed for safety and tolerability for a minimum of 24 weeks at the recommended dose. Assessment of changes in plasma HIV RNA levels and in CD4+ cell counts was also conducted. To assess resistance, information was collected and assessed regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving raltegravir potassium, particularly from those who experience loss of virologic response.

6 Review of Efficacy

Efficacy Summary

IMPAACT Trial P1066 was an open-label, non-comparative trial in which pediatric subjects (mostly treatment-experienced) were stratified into cohorts based upon age (≥ 12 to < 19 years; ≥ 6 to < 12 years; and ≥ 2 to < 6 years). The oldest cohort received the marketed adult raltegravir tablet, and the youngest cohort received the new chewable raltegravir tablet formulation. Cohort II (≥ 6 to < 12 years) had two parts: Cohort IIA received the adult tablet, and Cohort IIB received the chewable tablet.

Stage I was a dose-finding period during which evaluation of safety and tolerability was conducted in a limited number of subjects. Evaluation of steady state concentration profiles and pharmacokinetic profiles was also conducted in order to demonstrate if pediatric raltegravir exposures approximated adult exposures, and to explore exposure-response relationships. Stage II of the trial was the chronic dosing period in which longer term evaluation of safety and tolerability of the final selected doses of raltegravir (with OBT) was conducted, up to 24 weeks. The evaluation of similar information was conducted up to 48 weeks.

Raltegravir adult tablets and chewable tablets, in combination with OBT, demonstrated good antiviral activity over the 24 week trial period. Overall, 51/96 (53.1%) of trial subjects achieved an HIV RNA level < 50 copies/mL by Week 24, and 65/96 (65.6%) of subjects achieved an HIV RNA level < 400 copies/mL by Week 24. Such results would be expected in a treatment-experienced HIV-infected population, as seen in other pediatric trials involving subjects who are treatment-experienced, and in this trial, which enrolled a large number of such subjects (21/96 subjects, or 22%, had a PSS of 0 or 1, and 33/96, or 34%, had a GSS of 0 or 1).

In Trial P1066, there did not appear to be any difference in virologic response based on subgroup analysis (age, race, baseline HIV RNA category, baseline CD4 cell count category), but there was a gender difference noted, with males having a higher virologic response rate than females. The reasons for this difference remained elusive after ad hoc analyses. The virologic response was durable to Week 48. The CD4 cell count and percent also increased over the 24-week trial period, and the response was durable to Week 48.

Table 5 summarizes the virologic responses to raltegravir treatment at Week 24.

Table 5. Virologic Response to Raltegravir Treatment (with OBT) at Week 24

Virologic Parameters	Virologic Response at Week 24
HIV RNA < 50 copies/mL	53%
HIV RNA < 400 copies/mL	66%
≥1 log drop or HIV RNA < 400 copies/mL	72%

6.1 Indication

The current ISENTRESS (raltegravir potassium) indication is for the treatment of HIV-1 infection in adult patients in combination with other antiretroviral agents. The applicant seeks to extend the indication to include pediatric patients 2 years of age and older.

6.1.1 Methods

The primary efficacy endpoints of the trial included the evaluation of the following parameters at Week 24:

1. Proportion of subjects achieving a 1-log drop from baseline in HIV RNA
2. Proportion of subjects achieving HIV RNA < 50 copies/mL
3. Proportion of subjects achieving HIV RNA < 400 copies/mL
4. The change from baseline in CD4 cell count (cells/mm^3)
5. The change from baseline in CD4 percent

Additional primary clinical endpoints included evaluation of the steady state plasma concentration profiles and PK parameters of raltegravir in infants, children and adolescents.

Analysis of the primary endpoint was conducted using the "snapshot" analysis, which is an efficacy analysis approach adopted by the FDA to produce results for virologic response that utilize only HIV RNA data at the visit of interest. Applicants are requested to conduct their primary analysis in HIV treatment trials using the snapshot analysis.

Medical Officer comment: In addition to the snapshot analysis, the applicant used other methodologies to analyze their primary analysis. These included the Observed Failure approach, in which those who prematurely discontinued assigned therapy due to lack of efficacy were considered failures, and those who did so for reasons other than lack of efficacy were excluded from the analysis (virologic endpoint), and the Non-Completer = Failure approach, in which subjects who prematurely discontinued assigned treatment regardless of reasons, were considered as failures thereafter (study endpoint). The applicant used the Observed Failure approach as the primary approach for all efficacy analyses, and the Non-Completer = Failure approach as the sensitivity analysis.

Virologic failure was defined as follows:

1. Never achieved ≥ 1 log drop from baseline in plasma HIV RNA or HIV RNA < 400 copies/mL through Week 24, or
2. Virologic rebound at Week 24 or later is defined as (a) confirmed HIV RNA ≥ 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 400 copies/mL; Or (b) confirmed > 1.0 $\log_{10}$ increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart). Nadir is defined as the lowest HIV RNA by the evaluated time point.

In addition to virologic parameters, immunologic parameters (CD4 cell count and percent), and resistance data, were also assessed as part of the efficacy evaluation.

6.1.2 Demographics

The main demographic characteristics of the trial population are shown in Table 6, and baseline clinical characteristics are shown in Table 7. A total of 96 subjects were included in the Final Dose (FD) population. The median age was 13 years (range, 2 to 18), and gender distribution was fairly well-balanced, with 49 % male, and 51 % female. The majority of enrolled subjects were Black/African-American (59.4 %), followed by Whites (34.4 %), Unknown race (4.2 %), American Indian (1 %) and Multi-racial (1%).

Of note, the classification of race/ethnicity internationally may differ from that in the United States. For example, multiracial individuals in South Africa are known as 'coloureds', whereas in the US, these individuals might be classified as Black/African-American. This disparity likely only affected the classification of only a few subjects. In addition, the majority of subjects enrolled were Black/African-American (59%), and were mostly enrolled from the US. This is borne out also in other factors, such as the predominant viral subtype (see Table 7).

Table 6. Subject Baseline Demographics 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 (%)
Age (years)					
Mean (SD)	15.2 (1.9)	10 (1.4)	8.8 (1.6)	3.2 (1.2)	11.6 (5.2)
Median	15	10.5	9	3	13
Range	12 - 18	8 - 11	6 - 11	2 - 5	2 - 18
Gender					
Male	30 (51)	3 (75)	7 (54)	7 (35)	47 (49)
Female	29 (49)	1 (25)	6 (46)	13 (65)	49 (51)
Race					
Black/African-American	35 (59)	3 (75)	7 (54)	12 (60)	57 (59.4)
White	21 (36)	1 (25)	6 (46)	5 (25)	33 (34.4)
American Indian	1 (2)	0	0	0	1 (1)
Multi-racial	0	0	0	1 (5)	1 (1)
Unknown	2 (3)	0	0	2 (10)	4 (4.2)
Ethnicity					
Hispanic/Latino	22 (37)	1 (25)	7 (54)	8 (40)	38 (40)
Not Hispanic/Latino	34 (58)	2 (50)	6 (46)	9 (45)	51 (53)
Unknown	3 (5)	1 (25)	0	3 (15)	7 (7)

Baseline HIV Characteristics

In terms of subjects' baseline clinical characteristics, the CDC HIV Clinical Classification was fairly balanced, with Class A - 28 %, Class B - 29%, and Class C - 30%; the remainder (Class N) numbered 13 percent. Seventy-two percent of subjects were infected with viral subtype clade B (72 %). In terms of baseline plasma HIV RNA, most subjects (60 %) were moderately virally suppressed, with HIV RNA > 4,000 to ≤ 50,000 copies/mL, while only 8 % of subjects had HIV RNA >100,000 copies/mL. Median baseline CD4 cell count was 481 cells/mm3, while median CD4 percent was 23 %, with the range being 0 to 44 percent.

The majority of enrolled subjects across treatment groups were relatively virologically suppressed, as suggested by the low number of subjects with plasma HIV RNA > 100,000 copies/mL. Given the natural history of HIV infection in pediatric patients, one might have expected a larger proportion of the younger children to have higher HIV viral loads, though the lower viral loads seen in the trial are likely explained by the fact that subjects were treatment-experienced. The CD4 percentages provide evidence of moderate viral suppression for all treatment groups. The predominance of Clade B suggests enrollment of subjects mostly from North America and Europe, which was the case.

Table 7. Subject Baseline Clinical Characteristics 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 (%)**
CDC HIV Clinical Classification					
A	14 (24)	2 (50)	6 (46)	5 (25)	27 (28)
B	24 (41)	0	3 (23)	1 (5)	28 (29)
C	21 (35)	1 (25)	0	7 (35)	29 (30)
N	0	1 (25)	4 (31)	7 (35)	12 (13)
Viral Subtype					
Clade B	54 (91)	2 (50)	6 (46)	7 (35)	69 (72)
Non-clade B[†]	4 (7)	2 (50)	7 (54)	12 (60)	25 (26)
Unknown	1 (2)	0	0	1 (5)	2 (2)
Baseline Plasma HIV RNA (copies/mL)					
0 to ≤ 4,000	9 (15)	1 (25)	1 (8)	2 (10)	13 (14)
> 4,000 to ≤ 50,000	36 (61)	2 (50)	9 (69)	11 (55)	58 (60)
> 50,000 to ≤ 100,000	10 (17)	1 (25)	2 (15)	4 (20)	17 (18)
> 100,000	4 (7)	0	1 (8)	3 (15)	8 (8)
Baseline CD4 Count (cells/mm^3)					
Mean (SD)	398 (230)	851 (510)	578 (270)	1115 (550)	592 (442)
Median	397	807	529	1087	481
Range	0 - 872	274 - 1515	16 – 1000	323 – 2361	0 - 2361
Baseline CD4 percentage					
Mean (SD)	20 (10)	25 (9)	29 (10)	28 (3)	23 (10)

	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Median	20	28	33	29	23
Range	0 – 44	13 – 32	2 – 40	13 – 42	0 - 44

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.

Previous Antiretroviral Drug Use

The majority of subjects were quite experienced in terms of the number of antiretroviral drug classes previously used, with 67 % having used three or more drug classes in the past (Table 8). With the exception of one subject in Cohort III, none were treatment-naïve. Of note, there were 4 subjects in cohort III who had a history of use of one ARV (reason is unclear, but this may have represented the use of mother-to-child prophylaxis of HIV). Seventy-eight percent of subjects overall had previously used NNRTIs, with the youngest cohort having the least experience with this class of antiretroviral drugs, as might be expected. Similarly, 83 % of subjects had a history of prior PI use, with the youngest cohort having the least such experience.

Baseline HIV Resistance

Please see Clinical Microbiology review by Dr. Sung Rhee for further details. In summary, the Genotypic Sensitivity Score (GSS) and Phenotypic Sensitivity score (PSS) are defined as the total number of antiretroviral agents in a subject's OBT to which the subject's viral isolate showed genotypic or phenotypic sensitivity, respectively, based upon resistance testing performed prestudy or at screening. The majority of subjects in the FD population had a PSS of 2 (39 %), suggesting that subjects' isolates showed moderate antiretroviral sensitivity upon resistance testing at baseline (Table 8). Although the sample size was small, four subjects (30 %) in Cohort IIB had a PSS of 1, suggesting significant resistance in these young subjects. The GSS followed the same trend, with the majority of subjects (39%) having a score of 2. As might be expected, no subjects outside the oldest cohort had a GSS of 1, while Cohort I had five subjects (9 %) with a GSS of 1. The older subjects in this cohort likely had more exposure to antiretroviral drugs, and therefore a higher proportion of resistant HIV isolates.

Table 8. Baseline Antiretroviral Drug Use, 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 (%)
Number of ARV Classes Previously Used					
0	0	0	0	1 (5)	1 (1)
1	2 (4)	0	0	2 (10)	4 (4)
2	6 (10)	2 (50)	7 (54)	12 (50)	27 (28)
≥ 3	51 (86)	2 (50)	6 (46)	5 (25)	64 (67)
Subjects with Prior NNRTI Use	51 (86)	3 (75)	11 (85)	10 (50)	75 (78)
Subjects with Prior PI Use	57 (97)	3 (75)	8 (62)	12 (60)	80 (83)
Phenotypic Sensitivity Score (PSS) ‡					
0	3 (5)	0	0	0	3 (3)
1	11 (19)	1 (25)	4 (30)	2 (10)	18 (19)
2	23 (39)	0	7 (54)	7 (35)	37 (39)
≥ 3	18 (30)	2 (50)	1 (8)	6 (30)	27 (28)
Missing	4 (7)	1 (25)	1 (8)	5 (25)	11 (11)
Genotypic Sensitivity Score (GSS) ‡					
0	5 (9)	0	0	0	5 (5)
1	19 (32)	1 (25)	6 (46)	2 (10)	28 (29)
2	19 (32)	2 (50)	6 (46)	10 (50)	37 (39)
≥ 3	15 (25)	1 (25)	1 (8)	7 (35)	24 (25)
Missing	1 (2)	0	0	1 (5)	2 (2)

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

6.1.3 Subject Disposition

A total of 126 pediatric subjects (All Treated population) were enrolled in the trial, of which 96 comprised the Final Dose population who received the selected dose of raltegravir. As of the data cut-off date (February 14, 2011), there was a total of 28 subjects who discontinued either trial therapy or the trial itself (Table 9).

Table 9. Subject Disposition in Trial P1066

	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Off Trial Drug	**18 (31%)**	**0**	**0**	**1 (5%)**	**19 (20%)**
Protocol-Defined Clinical Event	1 (2%)	0	0	1 (5%)	2 (2%)
Pregnancy	3 (5%)	0	0	0	3 (3%)
Guardian consent withdrawn	1 (2%)	0	0	0	1 (1%)
Not able to attend clinic	1 (2%)	0	0	0	1 (1%)
Non-adherent	9 (15%)	0	0	0	9 (9%)
Other reason	3 (5%)	0	0	0	3 (3%)
Off Trial	**9 (15%)**	**0**	**0**	**0**	**9 (9%)**
Subject/parent unable to reach clinic	1 (2%)	0	0	0	1 (1%)
Subject/parent withdrew consent prior to trial completion	1 (2%)	0	0	0	1 (1%)
Subject/parent unwilling to adhere to trial requirements	6 (10%)	0	0	0	6 (6%)
Other reason	1 (2%)	0	0	0	1 (1%)
TOTAL	**27 (46%)**	**0**	**0**	**1 (5%)**	**28 (29%)***

*Applicant noted total of 30 subjects; reviewer found total 28 subjects

The reasons for withdrawal in Table 9 did not include adverse events. The main reason for discontinuation of the trial drug, and for discontinuation from the trial, was non-adherence to the drug regimen. The total of 28 subjects comprised those who were enrolled up until the data cut-off date of February 14, 2011, and not simply the first 24 weeks of subject treatment.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoints, as noted in Section 6.1.1, included the evaluation of virologic factors (HIV RNA < 50 and < 400 copies/mL) and immunologic factors (change in CD4 cell count and percent) at Week 24. Primary endpoints also included evaluation of plasma PK profiles and parameters.

Results

The FDA's snapshot algorithm was utilized for calculating the primary endpoint i.e. defined as the proportion of subjects achieving HIV RNA < 400 copies/mL and < 50 copies/mL at Week 24. The results are shown in Table 10.

Table 10. Virologic Outcome at 24 Week Window (Window 18 – 30)

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%)

*Single death (Subject PID 503661) occurred at Day 597, and drug discontinued the same day
**Subject PID 503661: no HIV RNA data at 24 or 48 weeks, but PK data included in trial analysis

A total of 72% of subjects had a ≥ 1 log drop or HIV RNA < 400 copies/mL. The efficacy evaluation of virologic success completed by the applicant yielded results that were essentially the same as those calculated using the snapshot algorithm. The applicant determined that 53.7% of subjects had HIV RNA < 50 copies/mL and 66.3% had HIV RNA < 400 copies/mL at Week 24. Virologic data were missing for a single subject (PID 503661), for whom no HIV RNA data were included in the dataset for 24 weeks or 48 weeks.

The efficacy of raltegravir demonstrated in this trial was comparable to that noted in adult trials, namely the BENCHMRK I and 2 trials, which were Phase 3 trials designed to evaluate safety and antiretroviral activity of Isentress with OBT versus OBT alone in subjects with documented resistance to at least one drug class (NNRTIs, NRTIs, PIs). Through a pooled analysis of the two adult trials, efficacy (proportion of subjects with HIV RNA < 50 copies/mL) at 24 and 96 weeks was 63% and 55%, respectively, in the Isentress plus OBT arm. At Week 24 of this pediatric trial, the proportion of subjects with HIV RNA < 50 copies/mL was 53%, while the proportion of subjects with HIV RNA < 400 copies/mL was 66 percent.

The proportion of pediatric subjects with HIV RNA >50 copies/mL at Week 24 was 44/96 (46%), and the reasons for failure are likely to be due to multiple reasons, including poor adherence leading to inadequate exposure and potentially development of resistance, as well as PSS of 0 at baseline.

The mean change in CD4 cell count from baseline to Week 24 was 205 while the mean change in CD4 percent was 5.0. Of note, the results from the applicant were slightly different but did not lead to a different conclusion of the outcome.

Evaluation of Pharmacokinetic Parameters

Please see Section 4.4.3 and Clinical Pharmacology review by Dr. Ruben Ayala for further details. In summary, the main pharmacokinetic targets of raltegravir in this pediatric trial 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. In addition, doses were targeted to deliver geometric mean C_{12h} values greater than 33 nM, which corresponds to the *in vitro* IC_{95} value. All proposed pediatric doses did lead to adequate exposures of raltegravir.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints (Section 6.1.1.) focused on the safety and tolerability of raltegravir use in pediatric subjects at the final selected dose in combination with OBT during the chronic dosing phase, over 48 weeks. Given the fact that the sponsor has not yet submitted the complete data from this ongoing chronic dosing phase (all of the Week 48 data from Cohorts I, IIA and IIB, and 50 % of the data from Cohort III were submitted), data from a total of 71 subjects were available for analysis.

Virologic parameters at Week 48 determined by the applicant were similar to those found by this reviewer.

6.1.6 Other Endpoints

The tertiary endpoints, which comprised the evaluation of safety and efficacy of raltegravir in subjects treated for more than 48 weeks, were not assessed in this review.

Exposure-response: As no exposure-response had been previously identified in the adult population, no exposure-response relationship was thought to exist in the pediatric population.

Resistance development:

Please see Section 4.2 and Clinical Microbiology review by Dr. Sung Rhee.

Emergence of raltegravir resistance monitoring was done on 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). Resistance testing was done if subjects had HIV RNA >1000 and discontinued at Week 24 or later. Among the raltegravir treatment failure subjects (as defined above), 31 subjects had any 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%).

6.1.7 Subpopulations

Analysis by PSS score

The efficacy of raltegravir was analyzed by PSS score (Table 11). One would expect that the lower the PSS (i.e. the fewer antiretroviral drugs to which the subject's isolate is sensitive), the lower the virologic success would be, and vice versa. This trend did not appear to manifest, largely due to the amount of missing PSS data. Eleven subjects had no PSS score reported. Few conclusions can be drawn, therefore, regarding the effect of PSS on efficacy when stratifying by this factor. Stratification by PSS category (i.e. < 2 and ≥ 2), as performed by the applicant and corroborated by this reviewer (
Table 12), produced the same trend, i.e. the more treatment-experienced subjects were (lower PSS), the higher the virologic success (which is paradoxical). Had the missing PSS values been available, the trend may have been more in the direction expected, with more treatment experience leading to lower efficacy.

Table 11. Efficacy Stratified by Phenotypic Sensitivity Score (PSS)*

Virologic Parameter at Week 24	PSS = 0 N=3 n (%)	PSS = 1 N=18 n (%)	PSS = 2 N=37 n (%)	PSS = ≥ 3 N=27 n (%)	Missing PSS values (N=11)
HIV RNA < 50 copies/mL	2 (66)	12 (67)	20 (54)	11 (41)	6
HIV RNA < 400 copies/mL	2 (66)	15 (83)	25 (68)	13 (48)	8

Table 12. Efficacy Stratified by PSS Category

Virologic Parameter at Week 24	PSS < 2 N=21 n (%)	PSS ≥ 2 N=64 n (%)	Missing PSS values (N=11)
HIV RNA < 50 copies/mL	14 (67)	31 (48)	6
HIV RNA < 400 copies/mL	17 (81)	38 (59)	8

Analysis by Baseline HIV RNA Category

The efficacy of raltegravir was analyzed by baseline HIV RNA category. Although stratification by baseline HIV RNA </> 100,000 copies/mL would have been preferred, only 8 subjects had baseline HIV RNA >100,000 copies/mL. Therefore analysis was stratified by HIV viral load of ≤ 50,000 copies/mL or > 50,000 copies/mL (Table 13). The virologic response appears to be higher in subjects whose baseline HIV RNA category was > 50,000 copies/mL, in all three parameters measured. However, interpretation of this result should be with caution as the result may have been skewed due to the small number of subjects. Despite this finding, the response rate was still significant in subjects who were found at baseline to have viral loads lower than or equal to 50,000 copies/mL.

Table 13. Efficacy Stratified by Baseline HIV RNA Category

Virologic Parameter at Week 24	≤ 50,000 copies/mL N=71 n (%)	> 50,000 copies/mL N=25 n (%)
HIV RNA < 50 copies/mL	36 (51)	16 (64)
HIV RNA < 400 copies/mL	46 (65)	18 (72)

Analysis by Age

The efficacy of raltegravir was analyzed by age, using the cohort-based age stratifications: ≥ 12 to < 19 years; ≥ 6 to < 12 years (Cohorts IIA and IIB combined); and ≥ 2 to < 6 years (Table 14). The results suggest that age did not have an effect on the efficacy of raltegravir as measured at Week 24. The proportion of subjects with ≥1 log drop or HIV RNA < 400 copies/mL at Week 24 ranged from 73% in the oldest subjects, to 70% in the youngest. The proportion of subjects with HIV RNA < 50 copies/mL at Week 24 ranged from 56% in the oldest subjects, to 50% in the youngest, while the proportion of subjects with HIV RNA < 400 copies/mL at Week 24 was 64% in the oldest subjects, 65% in the next younger group of subjects, and 60% in the youngest subjects. This finding of general equanimity between the efficacy in the various age groups, which utilized different formulations of raltegravir (i.e. adult tablet in subjects ≥ 12 to < 19 years of age, primarily chewable tablet in subjects ≥ 6 to < 12 years of age, and chewable tablet in subjects ≥ 2 to < 6 years of age) suggests that the efficacy of the two raltegravir formulations was similar in this subject population.

Table 14. Efficacy Stratified by Age at Week 24

Virologic Parameter at Week 24	≥ 12 to < 19 years N=59 n (%)	≥ 6 to < 12 years N=17 n (%)	≥ 2 to < 6 years N=20 n (%)
HIV RNA < 50 copies/mL	33 (56)	9 (53)	10 (50)
HIV RNA < 400 copies/mL	41 (64)	11 (65)	12 (60)

Analysis by Gender

The efficacy of raltegravir was analyzed by gender (Table 15.), and a significant difference was found between males and females. The efficacy of raltegravir was found to be much higher in males at Week 24. A total of 43% of females experienced an HIV RNA < 50 copies/mL by Week 24, compared with 66% of males, while the proportion of subjects with HIV RNA < 400 copies/mL at Week 24 was 61% for females and 83% for males.

There are no data to support the notion that raltegravir works differently in pediatric (or adult) males and females, and none that suggests that efficacy should be enhanced in male subjects[1]. The applicant performed ad hoc analyses to explore the reason for the gender association with virologic response; consideration was given to drug formulation and adherence (based on pill count data) by adding each of these into the logistic regression model predicting virologic success.

The Applicant evaluated the distribution of the raltegravir sparse PK parameters C_{all} and GM C_{12hr} for females versus males in the Final Dose population. Mean values were similar for both genders, though there appears to be a higher incidence of low outlier values for females compared to males, particularly in Cohort I. These low outlier values represent subjects with concentration values that were below the assay limit of quantization (BLOQ); there was a slightly higher frequency of BLOQ values for females vs. males in the Final Dose population: 31% of females vs. 26% of males had at least 1 BLOQ value; 17% of females vs. 11% of males had multiple BLOQ values. This finding was largely driven by Cohort I, where 43%. This analysis suggests that the reason why this virologic association with gender was seen may have been due to differences in drug adherence, with males being more adherent to their drug regimens and therefore having a higher exposure and thus better virologic response rate. Given the trial design (open labeled and single arm) and the small sample size evaluated however, one should be cautious when interpreting this evidence. Importantly, a similar difference has not been noted in the adult raltegravir data.

Table 15.. Efficacy Stratified by Gender at Week 24

Virologic Parameter at Week 24	Females N=49 n (%)	Males N=47 n (%)
HIV RNA < 50 copies/mL	21 (43)	31 (66)
HIV RNA < 400 copies/mL	30 (61)	39 (83)

Analysis by Race

The efficacy of raltegravir through Week 24 was analyzed by race. The total number of subjects in each race classification varies considerably, so comparison of virologic response rates is

1 Brainhard DM, Wenning LA, Stone JA, Wagner JA, Iwamoto M. Clinical pharmacology profile of raltegravir, and HIV-1 integrase strand transfer inhibitor. J Clin Pharmacol 2011;51(10):1376-402

problematic. That said, a comparison of the response rates between Black/African Americans and Whites, who had the highest number of subjects, yields a percentage of 70 to 71% for both for ≥ 1 log drop or HIV RNA < 400 copies/mL. Few conclusions can be drawn regarding the differences in virologic response between the races in general with this trial, but experience has shown that there are few to no racial differences in the efficacy of raltegravir based on race (Brainhard 2011).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose selection for raltegravir use in pediatric subjects in this trial was based upon pharmacokinetic parameters discussed in Section 4.4.3. Exploration of dosing was conducted during Stage I of the trial; the approach to selecting the final doses to be used in Stage II of the trial was to determine the pediatric dose that would approximate adult exposure at the 400 mg BID regimen, using the adult tablet formulation. Table 16 shows the rationale behind the dose selection.

Table 16. Final Dose Selection

Cohort	Age Range	RAL Formulation	Final Drug Dosage	Reason
I	12 – 18 years	Adult tab	400 mg BID	Weight-based dosing to approximate 6 mg/kg BID (200 to 600 mg BID)
IIA	6 – 11 years	Adult tab	400 mg BID (Wt ≥ 25 kg)	Weight-based dosing to approximate 6 mg/kg BID (200 to 600 mg BID)
IIB	6 – 11 years	Chewable tab	6 mg/kg BID (max 300 mg)	Weight-based dosing to approximate 8 mg/kg BID (75 to 300 mg BID)
III	2 - 5 years	Chewable tab	6 mg/kg BID (max 300 mg)	Weight-based dosing to approximate 8 mg/kg BID (75 to 300 mg BID)

In summary, the recommended dose of raltegravir for pediatric subjects is as follows:

Age 12 years and older: One 400 mg film-coated tablet twice daily, orally.

Age 6 to less than 12 years of age:

- If at least 25 kg in weight: One 400 mg film-coated tablet twice daily, orally, OR chewable tablets: Weight based (6 mg/kg twice daily) to maximum dose 300 mg, twice daily

- If less than 25 kg in weight: Chewable tablets: weight based to maximum dose 300 mg twice daily

Age 2 through 5 years of age: Chewable tablets: Weight based (6 mg/kg twice daily) to maximum dose 300 mg twice daily

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The treatment effect was durable to at least Week 48, as determined by the available data to that time point. The virologic response as measured by ≥ log drop or HIV RNA below 400 copies/mL, HIV RNA below 50 copies/mL, and HIV RNA below 400 copies/mL increased over time, as noted in evaluations conducted at Week 24 and at Week 48 (Sections 6.1.4 and 6.1.5.)

The extrapolation of efficacy for antiretroviral drugs like raltegravir is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[1] DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011, pp 1-279. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

7 Review of Safety

Safety Summary

Raltegravir administered with observed background treatment was, in general, safe and tolerable when used in pediatric subjects 2 years and older. The nature of the adverse events noted in pediatric subjects in this trial was similar to that of adult patients. The frequency of serious adverse events and nonfatal adverse events was relatively low in these pediatric subjects, though the frequency of serious adverse events was found to be, comparatively, slightly higher in pediatric subjects. This finding was largely due small numbers of pediatric subjects in the trial and the subsequent large proportions of adverse events seen. As a result, comparison with adult SAEs was therefore difficult. In terms of adverse events of interest, significant findings for metabolic disorders, IRIS, rash, serum AST and ALT, psychiatric disorders, and AIDS-defining conditions were very low in frequency. The nature of significant psychiatric disorders (suicidal ideation) was consistent with what has been seen in postmarketing with the use of raltegravir in adult patients.

The Safety Update Report submitted by the applicant evaluated reports of pediatric use of raltegravir over a three-year period (from time of initial market approval), and a total of 23 reports of pediatric use (1.3% of the total reports) were identified. A review of the cases did not suggest new safety issues with regards to raltegravir exposure in pediatric patients.

7.1 Methods

Safety data for this NDA supplement were provided by the applicant in the form of electronic datasets that contained tables of clinical adverse events. As previously agreed with the Division, the applicant did not provide an Integrated Summary of Safety (ISS), but rather submitted the CTD Summary of Clinical Safety that incorporated relevant integrated analyses that are usually found in the ISS.

Narrative summaries and case report forms were provided for all subjects who experienced one or more of the following: Deaths; all SAEs (drug-related and non-drug-related); and all drug-related AEs leading to withdrawal. Tabulations of AEs, SAEs, and study drug interruptions or discontinuations were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc.).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted using the data generated from the clinical trial under review. The safety profile of raltegravir has previously been established in adults using an adequate number of subjects to permit approval of the drug for marketing in 2007. IMPAACT Trial P1066/Merck 022 was a pivotal pediatric trial that was conducted to assess the safety, efficacy, tolerability and pharmacokinetics of raltegravir in HIV-infected pediatric subjects 2 years of age and older. Subjects were treatment-experienced, with the exception of a single subject in Cohort III. The primary objective of the trial was the evaluation of safety and efficacy of raltegravir in combination with OBT over a 24-week period. The primary therapy period lasted from September 14, 2007 to February 14, 2011. The initial treatment period was for 24

weeks, followed by an additional 24 weeks to evaluate chronic dosing with raltegravir and OBT. The Safety Update Report for raltegravir was submitted to the NDA in September 2011.

The pivotal pediatric trial provides an adequate number of subjects exposed to raltegravir to allow for an assessment of safety and tolerability.

7.1.2 Categorization of Adverse Events

The submitted data support the requirement of safety and tolerability of raltegravir in combination with OBT. A minimum of 46 subjects were required to be evaluated for safety at the to-be-marketed dose or higher of raltegravir for 24 weeks, and the applicant enrolled a total of 96 subjects who received the final selected dose of raltegravir. The submitted data were adequate with regard to the number of subjects exposed to raltegravir and the duration of exposure to the drug. The data were submitted by SAS transport file for analysis using JMP software. Adverse events were depicted using MedDRA preferred terms. All adverse events were graded using DAIDS standardized Toxicity Table for Grading Severity of Pediatric (>3 months of age) Adverse Events.

The part of the trial that includes subjects ≥ 4 weeks to < 2 years of age (Cohorts IV and V) is ongoing. Subjects are receiving oral raltegravir granules for suspension. An evaluation of the data for these subjects are to be submitted for review by January 5, 2015.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from across studies other than Trial P1066 was not conducted.

7.2 Adequacy of Safety Assessments

The monitoring of clinical and laboratory safety parameters in this study was considered adequate in light of the fact that raltegravir is an approved drug for which a significant amount of safety data (in adults) are available from previously-reviewed treatment protocols. A minimum of 46 pediatric subjects with 24 week data were requested by the Division, and the applicant submitted safety data on 96 subjects.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure was defined as the duration of time that a subject received active dosing of raltegravir, either overall or at a particular dose strength. The data cut-off date was February 14, 2011.

The mean number of days that Cohort I and IIA subjects took the adult raltegravir tablet formulation at 400 mg BID (800 mg/day) was 657 days (range, 28 to 1112). The mean number of days that Cohort IIB and III took the chewable raltegravir tablet formulation (approximately 6 mg/kg BID, to maximum of 300 mg BID) was 351 days (range, 179 to 604). The mean number

of days for all Final Dose subjects using either raltegravir formulation was 565 (range, 28 to 1112).

7.2.2 Explorations for Dose Response

Raltegravir drug dosing was based upon weight and age. Subjects ≥ 12 years to < 19 years received the adult raltegravir tablet formulation (400 mg BID). Subjects ≥ 6 to < 12 years either received the adult dose if at least 25 kg in weight, or chewable tablets based on weight (6 mg/kg BID). If less than 25 kg in weight, subjects in this age range received chewable tablets dosed by weight. Subjects ≥ 2 to < 6 years of age received the chewable tablet dosed by weight.

The administered doses of the chewable tablet ranged from 75 to 400 mg BID, and for the adult tablet ranged from 200 to 600 mg BID. These doses were within the protocol-defining dosing limits. Subjects who received higher doses of raltegravir than the to-be-marketed dose were too few to make any meaningful conclusions. Their AE profile, however, was similar to those who did receive the to-be-marketed dose.

7.2.3 Special Animal and/or In Vitro Testing

Isentress is an approved medication for treatment of HIV-1 infection in adults, and no additional animal or *in vitro* testing was therefore conducted for this NDA or supplement.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed in this trial, and testing was found to be adequate. Following a baseline evaluation, subjects were periodically evaluated for adverse events and laboratory parameters at screening, trial entry, re-entry (for subjects in Stage I who underwent a drug dose adjustment), Week 1 (Intensive PK visit), Safety Visit (for Stage I subjects whose dose was increased to the Stage II dose), Weeks 4, 8, 12, 24, 36, 48, 14-day post-therapy follow-up, and Early Discontinuation.

7.2.5 Metabolic, Clearance, and Interaction Workup

Trials studying metabolic, clearance and drug-drug interactions have previously been conducted for raltegravir, and were not part of this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no evaluations for potential adverse events for similar drugs in the same drug class as raltegravir.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths that occurred from Week 0 to Week 24. There was a single death that occurred during the trial, at Week 29. The subject experienced the serious adverse event of pneumonia, and this was deemed by the investigator to be unrelated to raltegravir.

Narrative: The subject was a 15 year old black female with a medical history significant for chronic anemia, severe failure to thrive and HIV wasting syndrome, recurrent upper respiratory infection and recurrent oral candidiasis, who died as a result of bilateral pneumonia. She was placed on trial therapy of raltegravir 200 mg orally BID adult tablet on July 8, 2008. Based on the per-protocol dose adjustment for the cohort, the subject was switched to raltegravir 400 mg BID adult tablet November 24, 2008. Optimized background regimen included lopinavir/ritonavir, abacavir sulfate, and lamivudine, while concomitant therapy included trimethaprim/sulfamethoxazole (TMP/SMX) and azithromycin. Subject was seen in the ED on (b) (6) with complaints of severe back pain, cough, anorexia, respiratory distress, weight loss, and diarrhea. HIV RNA was > 100,000 copies/mL and CD4 cell count was 15 (1%). The subject was hospitalized and treated with TMP/SMX, fluconazole, and other medications. Five days later, respiratory distress worsened and lactate dehydrogenase increased; TMP/SMX was discontinued and pentamidine was initiated. Follow-up chest radiograph showed bilateral pneumonia with new bilateral pleural effusions with pulmonary edema and bilateral lung consolidation. The subjects expired that day, and the cause of death (severe respiratory distress due to bilateral pneumonia) was deemed to be unrelated to trial medication.

The cause of death in this subject with a complicated medical history was not likely due to the trial medication, as noted by the applicant. Given the subject's significant level of immunosuppression (CD4 cell percent was 1%, and HIV RNA was > 100,000 copies/mL), she was at risk of substantial morbidity secondary to infections, both opportunistic and otherwise. Pneumonia, pleural effusions, and pulmonary edema (etiologies of subject's death) have not been noted as treatment-related adverse events in past trials using raltegravir, nor have they been noted in postmarketing surveillance.

Table 17. Listing of Clinical Adverse Events Leading to Death: All Treated Population

Cohort	Stage	Subject Number	Gender	Race	Age (years)	Dose (mg BID)	Relative Day of Onset	Adverse Event	Relative Day off Treatment	Grade	Drug Relationship	Action Taken	Outcome
I	I	502828	F	Black/ African American	15	0	597	Pneumonia	597	5	Not related	Permanently Discontinued	Death

Grade I = Mild, 2 = Moderate, 3 = Severe, 4 = Life-Threatening, 5 = Death
Events were included if they occurred while on trial drug or within 14 days after discontinuation of trial drug

7.3.2. Nonfatal Serious Adverse Events

A total of 16 serious adverse events (SAEs) were reported in 13 FD subjects (14%) during Weeks 0 to 24 (Table 18). The category with the highest frequency of reported SAEs was infections and infestations (9 subjects). There were otherwise relatively few SAEs reported, with three subjects developing pneumonia (3%), and two subjects each (2%) exhibiting suicidal behavior and lobar pneumonia. Notably, the majority of these SAEs occurred in the older subjects, i.e. those in Cohort 1, who were taking the adult raltegravir tablet. Few SAEs occurred in younger children. The fact that so few SAEs were noted in younger children is reassuring. Cohort I enrolled not only the oldest subjects in the trial, but also the largest number of subjects and those with the longest drug exposure; therefore, it is expected that the frequency of SAEs would be higher in this cohort compared with the others.

In comparison to the adult BENCHMRK I and II trials using raltegravir, there was a higher proportion of SAEs that occurred at a frequency of ≥ 2 percent in this pediatric trial. The majority of the SAEs categories are infection and infestations, which in general tend to occur more frequently in children compared to adults. This may explain why there were more SAEs reported in children. The number of subjects in this trial was, however, smaller, so proportions were larger than in the adult trials, making comparison difficult. With infections and infestations excluded, the SAE profile in children appears to be similar to that of adults.

Table 18. Nonfatal Serious Adverse Events by Cohort, Weeks 0 to 24

Preferred Term	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Acute renal failure	1 (2%)	0	0	0	1 (2%)
Allergic dermatitis	0	0	0	1 (5%)	1 (2%)
Asthma	1 (2%)	0	0	0	1 (2%)
Bronchopneumonia	0	0	0	1 (5%)	1 (2%)
Infection	1 (2%)	0	0	0	1 (2%)
Lobar pneumonia	1 (2%)	0	0	1 (5%)	2 (4%)
Metrorrhagia	1 (2%)	0	0	0	1 (2%)
Pneumonia	3 (5%)	0	0	0	3 (3%)
Pyrexia	1 (2%)	0	0	0	1 (2%)
Suicidal ideation	2 (3%)	0	0	0	2 (4%)
Viral pneumonia	0	0	1 (8%)	0	1 (2%)
Viral respiratory tract infection	0	0	1 (8%)	0	1 (2%)

From Weeks 0 to 48, a total of 14 (15%) FD subjects experienced SAEs, adding an additional subject to the tally of subjects who experienced SAEs from Week 0 to 14.

Grade 3 and 4 Clinical Adverse Events

A total of 13 FD subjects (13.5%) exhibited Grade 3 or higher clinical AEs from Week 0 to 24. The highest frequency of Grade 3 and 4 clinical AEs occurred in the SOC Infections and Infestations (9%), including primarily various forms of pneumonia (Table 19). Of note, these subjects did not have low CD4 count or neutropenia as a risk factor for pneumonia. Three subjects displayed psychiatric AEs, including suicidal behavior (2) and psychomotor hyperactivity (1). Both episodes of suicidal behavior (PID 690747 and PID 720101) were deemed unrelated to raltegravir therapy, and neither resulted in discontinuation of trial drug. Both subjects had a antecedent trigger to their behavior, with no reported history of psychiatric issues. It appears unlikely that raltegravir was the causative factor in their psychiatric episodes. Refer to section below for further discussion of psychiatric events.

One subject (PID 690747) was an 18 year old male with no prior psychiatric history, swallowed six diphenhydramine capsules after an argument with his mother. He promptly induced vomiting, and suffered no ill effects. The other subject (PID 720101) was a 15 year old female with a reported history of "acting out," who placed a rope/cord around her neck after a disagreement with a family member. The subject was not harmed, and after being taken to the emergency department for evaluation, was not deemed to be suicidal or homicidal.

The Grade 3 and 4 clinical AEs that occurred were not unexpected in the enrolled subjects. Treatment-experienced HIV-infected patients are subject to a range of infections, pulmonary infections being prominent amongst these, as was reported in the trial. Again, the majority of Grade 3 and 4 infections (and the most significant of these) occurred in Cohort I, which comprised the oldest subjects (adolescents) who had been on trial drug the longest. Young children did not experience a large number of Grade 3 or 4 clinical AEs.

Table 19. Grade 3 and 4 Clinical Adverse Events

Preferred Term	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Acute renal failure	1 (2%)	0	0	0	1 (2%)
Abnormal behavior	1 (2%)	0	0	0	1 (2%)
Bronchopneumonia	0	0	0	1 (5%)	1 (2%)
Gastroenteritis	1 (2%)	0	0	1 (5%)	2 (4%)
Hyperlactacidemia	0	0	0	1 (5%)	1 (2%)
Impetigo	0	0	0	1 (5%)	1 (2%)
Influenza	1 (2%)	0	0	0	1 (2%)
Insomnia	1 (2%)	0	0	0	1 (2%)
Lobar pneumonia	1 (2%)	0	0	1 (5%)	2 (4%)
Lymphadenitis	1 (2%)	0	0	0	1 (2%)

Preferred Term	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Pharyngitis	0	0	1 (8%)	0	1 (2%)
Pneumococcal pneumonia	1 (2%)	0	0	0	1 (2%)
Pneumonia	3 (5%)	0	0	0	3 (3%)
Psychomotor hyperactivity	1 (2%)	0	0	0	1 (2%)
Pyrexia	1 (2%)	0	0	0	1 (2%)
RSV pneumonia	0	0	1 (8%)	0	1 (2%)
Suicidal ideation	2 (3%)	0	0	0	2 (4%)
Viral pneumonia	0	0	1 (8%)	0	1 (2%)
Viral respiratory tract infection	0	0	1 (8%)	0	1 (2%)

From Weeks 0 to 48, a total of 15 (16%) FD subjects experienced Grade 3 or 4 AEs, representing an additional two subjects who experienced such events between Week 24 and Week 48.

7.3.3 Dropouts and/or Discontinuations

There were no discontinuations that occurred due to either clinical or laboratory adverse events in the Final Dose populations.

7.3.4 Significant Adverse Events (Adverse Events of Interest)

There were no prespecified significant adverse events in the pediatric trial protocol. There were, however, adverse events of particular interest, as noted in the adult data applications for raltegravir. These included metabolic disorders, immune reconstitution syndrome (IRIS), rash, AST/ALT elevations, psychiatric disorders, and AIDS-defining conditions. They were included in the submission to provide additional information regarding their potential occurrence in pediatric subjects receiving raltegravir. In comparison with the adult raltegravir safety profile, no new safety signals were identified in the pediatric data. Data were evaluated from Week 0 to Week 48.

Metabolic Disorders

Metabolic disorders were reviewed in this application due to the common occurrence of dyslipidemias as complications of antiretroviral therapy, and because subjects had extensive prior and concurrent antiretroviral drug use, including use of PIs. Serum samples for lipids and glucose were not, however, routinely collected in the trial under fasted conditions.

Metabolic adverse events were reported in a total of 6 FD subjects (6%), and included decreased appetite (4 subjects), failure to thrive (1), hyperlactacidemia (1), and lactic acidosis (1). Serum dyslipidemias were infrequent, and were not reported from Week 0 to 24. Through Week 48, 10

subjects (10%) developed increased serum cholesterol, and 8 subjects (8%) developed increased low-density lipoprotein.

Immune Reconstitution Syndrome (IRIS)

Immune reconstitution syndrome refers to the development of an inflammatory response to indolent infections that may occur in patients during the initial phase of HIV treatment. There were no reports of IRIS in FD subjects.

Rash

Rash was noted in 12 FD subjects in the trial, including rash (4 subjects), allergic dermatitis (4), generalized rash (2), macular rash (1) and papular rash (1). These manifestations were confounded by the concurrent use of nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir, and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs), many of which are associated with rash. Given the significant frequency of rash in adults on antiretroviral drugs, the frequency in pediatric subjects in this trial appears to be quite low in comparison. Rash occurred more commonly in treatment-experienced adult subjects receiving regimens containing Isentress + darunavir/ritonavir compared to subjects receiving Isentress without darunavir/ritonavir or darunavir/ritonavir without Isentress. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

AST/ALT Elevations

AST and ALT elevations were fairly common, but were usually transient. For that reason, the elevations of note were those ≥ Grade 3. One FD subject (1%) experienced an ALT elevation of Grade 3 or greater, and one FD subject had a Grade 3 or greater AST elevation by Week 24. Subject PID 892125 had elevated serum AST and ALT deemed an SAE possibly related to raltegravir use (per the investigator) noted on Day 17. The maximum values of AST and ALT were 219 U/L (Grade 4) and 206 U/L (Grade 3). These values decreased soon after removing lamivudine and didanosine from the subject's OBT regimen (that included abacavir and efavirenz), but remained elevated. During a subsequent episode of pneumonia during Week 176, bilirubin was checked on several occasions, and always remained below Grade 1 during trial treatment. Raltegravir treatment was continued throughout. The transaminase elevation, therefore, appeared to be at least partially related to concomitant medications. Such a scenario would not be out of the ordinary in the subjects, given their OBT regimens.

Psychiatric Disorders

Given postmarketing reports of psychiatric adverse events (at a frequency of < 2%) with the use of the currently marketed raltegravir, including depression (particularly in subjects with a pre-existing history of psychiatric illness), and suicidal ideation and behavior, psychiatric disorders were explored in depth.

At baseline,16 FD subjects (17%) were found to have a secondary diagnosis of psychiatric disorders (e.g. 4 subjects (4%) had major depressive disorder). From Weeks 0 to 48, a total of 10 FD subjects (10%) were reported to have clinical adverse events of psychiatric disorders. Adjustment disorder, anger, attention deficit hyperactivity disorder (ADHD), insomnia, mood swings, restlessness, and sleep terror were each reported in one subject; suicidal behavior was reported in two subjects; abnormal behavior was reported in two subjects; and depression was reported in three subjects. Grade 3 psychiatric adverse events were reported in three FD subjects, and these events included suicidal ideation (2 subjects) and psychomotor hyperactivity (1 subject). The latter subject (PID 8501553) was a 12 year old male with no prior psychiatric history, who developed abnormal behavior, insomnia, and Grade 3 psychomotor hyperactivity, which was considered to be possibly related to raltegravir use.

The narratives of the two subjects who experienced suicidal ideation are as follows (both events were considered to be unrelated to raltegravir use):

- PID 690747: 18 year old male with no prior psychiatric history, who swallowed 6 diphenhydramine capsules after an argument with his mother. He promptly induced vomiting, and suffered no ill effects.
- PID 720101: 15 year old female with a reported history of "acting out," who placed a rope/cord around her neck after a disagreement with a family member. The subject not harmed, and was taken to the ED for evaluation and was not deemed suicidal or homicidal.

In summary, it appeared that most of the psychiatric disorders noted in the trial, and particularly suicidal ideation and psychomotor hyperactivity, occurred in the setting of confounding factors such as prior psychiatric diagnoses, prior acting out behavior, and concurrent stressors. From the data evaluated in this small trial, it does not appear that raltegravir use led to an increased risk of psychiatric disorders.

AIDS-Defining Conditions (ADC)

There were no ADCs that occurred from Week 0 to 48. A single subject (PID 502828) was found to have a new AIDS-defining condition, namely Category C ADC of wasting syndrome that occurred after Week 48.

7.3.5 Submission Specific Primary Safety Concerns

See 'Adverse Events of Interest' above.

7.4 Supportive Safety Results

Common Adverse Events

Common clinical AEs occurred in 77 FD subjects (80%) from Week 0 to 48, with the highest frequency of such AEs occurring in the SOC Infections and Infestations. Table 20Table 20 shows the range of common clinical AEs (excluding infections and infestations, malignancies, and laboratory AEs) exhibited in the trial. Cough was prominent (41%), as was pyrexia (32%), rhinorrhea (26%), and nasal congestion and vomiting (20% each).

Table 20. Summary of Common Clinical Adverse Events by Cohort, Weeks 0 to 24

Adverse Events Preferred Term	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
Abdominal pain**	15 (25%)	1 (25%)	1 (8%)	0	15 (16%)
Anger	0	1 (25%)	0	0	1 (1%)
Breath odor	1 (2%)	0	2 (15%)	0	3 (3%)
Cough	28 (47%)	2 (50%)	5 (38%)	6 (30%)	41 (43%)
Diarrhea	9 (15%)	0	0	4 (20%)	13 (14%)
Dizziness	6 (10%)	0	0	0	6 (6%)
Ear pain	9 (15%)	0	1 (8%)	1 (5%)	11 (11%)
Eczema	1 (2%)	0	2 (15%)	1 (5%)	4 (4%)
Headache	10 (17%)	2 (50%)	0	0	12 (13%)
Hepatomegaly	0	0	0	3 (15%)	3 (3%)
Macule	1 (2%)	0	0	2 (10%)	3 (3%)
Mood swings	0	1 (25%)	0	0	1 (1%)
Nasal congestion	14 (24%)	1 (25%)	3 (23%)	2 (10%)	20 (21%)
Nausea	11 (19%)	0	0	0	11 (11%)
Oropharyngeal pain	13 (22%)	0	3 (23%)	0	16 (17%)
Otorrhea	2 (3%)	0	0	2 (10%)	4 (4%)
Pyrexia	18 (31%)	1 (25%)	6 (46%)	6 (30%)	31 (32%)
Rash	2 (3%)	1 (25%)	3 (23%)	0	4 (4%)
Rhinorrhea	19 (32%)	0	3 (23%)	4 (20%)	26 (27%)
Vomiting	14 (24%)	0	1 (8%)	5 (25%)	20 (21%)
Wheezing	6 (10%)	1 (25%)	1 (8%)	2 (10%)	9 (9%)

*Excludes infections and infestations, malignancy, and lab AEs
**Abdominal pain includes upper abdominal pain

From Week 0 to 48, 82 (85%) FD subjects experienced common clinical AEs.

A significant majority of subjects experienced clinical AEs, but most of these AEs were not classified as serious or Grade 3 or higher. The Isentress label cites rates of common AEs in adult

patients in treatment studies. Common AEs that occurred at an incidence of < 2% in treatment-experienced and treatment-naïve subjects, that were also reported in Trial P1066, included abdominal pain, nausea, vomiting, headache, and dizziness. There are no significant AEs reported in this trial that have not been noted previously with raltegravir use.

7.4.2 Laboratory Findings

Grade 3 or 4 Laboratory Adverse Events

A total of 13 FD subjects (14%) experienced Grade 3 or 4 laboratory AEs during Weeks 0 to 24. The most frequent laboratory abnormality with a Grade of 3 or higher was neutropenia (8 subjects), followed by increased blood bilirubin (3 subjects), as shown in Table 21..

Table 21. Grade 3 and 4 Laboratory Adverse Events by Preferred Term, Weeks 0 to 24

Grade 3 or 4 Laboratory Adverse Events Preferred Term	Cohort I N=59 n (%)	Cohort IIA N=4 n (%)	Cohort IIB N=13 n (%)	Cohort III N=20 n (%)	Total N=96 n (%)
ALT increased	0	0	0	1 (5%)	1 (1%)
AST increased	0	0	0	1 (5%)	1 (1%)
Blood bilirubin increased	2 (3%)	1 (25%)	0	0	3 (3%)
Blood creatinine increased	1 (2%)	0	0	0	1 (1%)
Blood glucose decreased	0	0	0	1 (5%)	1 (1%)
Blood magnesium decreased	1 (2%)	0	0	0	1 (1%)
Blood pH abnormal	0	0	0	1 (5%)	1 (1%)
Neutrophil count decreased	5 (8%)	0	0	3 (15%)	8 (8%)

Blood bilirubin increased: blood bilirubin increased + hyperbilirubinemia
Neutrophil count decreased: neutrophil count decreased + neutropenia

A total of 15 (16%) FD subjects were reported to have Grade 3 or 4 laboratory AEs in the period Weeks 0 to 48.

Grade 3 and 4 laboratory AEs occurred at a low frequency in the initial 24 weeks of the trial. Similar laboratory AEs have been noted in treatment-experienced adult patients, as noted in the raltegravir labeling, which includes neutropenia, low hemoglobin, thrombocytopenia, hyperglycemia, hyperbilirubinemia, increased ALT and AST, increased alkaline phosphate, increased amylase, increased lipase, and increased creatine kinase as Grade 3 or higher laboratory AEs that occurred in trials comparing raltegravir to placebo. Further laboratory AEs became evident in Trial P1066 after Week 24, but these were few. It should be noted that the majority of Grade 3 and 4 laboratory AEs occurred in Cohort I, which, as mentioned earlier,

comprised older subjects and those who had been taking the trial drug for the longest period of time.

7.4.3 Vital Signs

All enrolled subjects had vital signs assessed as part of the initial workup, and vital sign collection was performed per protocol at each trial visit. The applicant provided summary statistics for vital signs. There were no significant abnormalities reported.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained as a routine part of the assessments carried out in this trial. Please refer to the original NDA review for details of cardiovascular evaluations.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

Immunogenicity was not assessed in this trial.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A formal assessment of exposure-safety was not conducted for this pediatric trial. See Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

Adverse events were assessed throughout treatment period. No specific time-dependency was identified.

7.5.3 Drug-Demographic Interactions

Raltegravir use was evaluated in pediatric subjects in this trial, and subjects were stratified by age (≥2 to < 6 years, ≥6 to < 12 years, and ≥ 12 to < 19 years). As previously mentioned (Section 7.2.2), a lower response rate (~ 44%) was noted in subjects enrolled in Cohorts I and IIA (i.e. subjects who took the adult raltegravir tablet formulation), with lower C_{12hr} levels being seen (median 115 nM, range 25 to 178 nM). The reasons for this disparity are unclear, and may have included medication non-adherence or high PK variability.

7.5.4 Drug-Disease Interactions

As with adults who take raltegravir, it appears that HIV disease was treated appropriately with the administration of raltegravir and OBT. This was evidenced by the general decrease in HIV-1 RNA level in subjects over time during the treatment period, as well as the improvement in CD4 cell count and percent. These changes occurred across cohorts and age groups.

7.5.5 Drug-Drug Interactions

All subjects were on more than one other drug during the trial (OBT). No formal assessment was made of the drug interactions between Isentress and these other drugs, but it is expected that drug-drug interactions in pediatric subjects will not be significantly different from those seen in adults (please see Raltegravir label).

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

Not applicable. See original NDA review

7.6.2 Human Reproduction and Pregnancy Data

Raltegravir is classified as Pregnancy Class C. Additional details can be found in the original NDA review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Both weight gain and age-appropriate increases in height were reported over the course of the trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known withdrawal or abuse potential with raltegravir. There is no information on overdoses in pediatric patients.

7.7 Additional Submissions / Safety Issues

Safety Update Report

A Safety Update Report was submitted to the NDA as part of this application. A summary of the information contained thereof follows.

The applicant provided a report on the Pediatric Post-marketing data for Raltegravir Tablets, for 2010. The report began with a review of the methods used to summarize the post-marketing experience from the Merck Worldwide Adverse Experience System (WAES) database, followed by the results that included an overall summary/reporting rate of post-marketing adverse experiences, the age and gender of pediatric patients with adverse experiences, a review of these pediatric adverse experiences by System Organ Class (SOC) and those most frequently reported, and a review of the reported adverse experiences in pediatric patients that are included as safety concerns in the raltegravir Risk Management Plan (RMP).

The Merck WAES database serves as a repository for the reporting of serious adverse experiences and adverse experiences of special interest from clinical trials, including expanded access programs, reports from the medical literature, and all adverse experiences from marketed use that are reported to Merck & Co., Inc. Reports are submitted voluntarily to the Company by health care providers, agencies, and consumers. The data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information, and incidence rates cannot be accurately calculated from data generated in the post-marketing environment.

The WAES database was searched on February 21, 2011, for all postmarketing (health care provider and consumer) reports in patients less than 18 years of age as reported in the designated age field from September 27, 2007 through December 31, 2010 with raltegravir as the primary suspect therapy. A narrative search was also performed via the WAES database in order to identify reports in which a specific age was not reported in the age field, but rather where general narrative text terms indicative of a patient less than 18 were used. The search included adolescent, baby, boy, child, children, daughter, girl, infant, kid, neonate, newborn, pediatric, son, teenager, and toddler.

An estimate of raltegravir use in the pediatric population could not be determined from the available data. The Company's Worldwide Financial Reporting System (WFRS) is a global repository for drug distribution data that is tabulated monthly for Merck marketed products. From 27-Sep-2007 through 31-Dec- 2010, the total number of 400 mg tablets of raltegravir distributed worldwide was (b) (4) Assuming each patient takes the recommended dosing of 2 tablets daily (800 mg), the estimated patient-years of exposure is (b) (4) which is possibly an overestimate as the total partly represents distributer stocking of inventory, or use in some expanded access programs. It is unknown how many of these patient-years of exposure are from pediatric patients.

A total of 1,755 (735 [42%] serious) adverse experience reports for raltegravir were identified in the WAES database from the time of first market approval, on 27-Sep-2007, through 31-Dec-2010. This included all reports of postmarketing use, as well as reports of compassionate use, named-patient, and temporary-use authorization that were not part of Merck clinical trials. Thus, the estimated reporting rate for raltegravir postmarketing and "compassionate use" adverse experience reports during the time period reviewed is 77 reports per 10,000 treated patients and 32 serious reports per 10,000 treated patients. Of these 1,755 reports, 23 (1.3%) were in pediatric patients.

Of these 23 pediatric patients, 17 had information on specific ages. One (6%) of the reports was in pediatric patients <2 years of age, 3 (13%) reports were found in pediatric patients 6 to <12 years of age, 14 (61%) reports were found in pediatric patients 12 to <19 years of age, and 6 (26%) reports were in pediatric patients of unknown age. In the 17 reports with gender documented, there were 10 (58%) reports in females and 7 (41%) reports in males. The one patient <1 year of age was exposed to raltegravir *in utero* and was also treated with raltegravir dissolved in water for four weeks after birth. No adverse event was associated with this report.

The most commonly affected SOCs in pediatric patients were Surgical and medical procedures (39%), General disorders and administration site conditions (35%), Injury, poisoning and procedural complications (5%), and Psychiatric disorders (5%). The nine reports in the Surgical and medical procedures SOC all contained the term "off label use" Interestingly, the reported adverse event terms in the Psychiatric disorders SOC were intentional drug misuse (3), insomnia (2) and personality change (1).

The most frequently reported adverse events in pediatric subjects are noted in Table 22. The remaining most frequently reported adverse events in pediatric patients were reported singly. In addition, all of the serious events were reported singly without any reporting patterns and did not raise any new safety concerns for raltegravir.

Table 22. Raltegravir – Five Most Frequently Reported Adverse Events in Pediatric Patients 27-Sep-2007 to 31-Dec-2010

Five Most Frequent AEs	No. of Events
Off label use	9
No adverse event	8
Drug exposure during pregnancy	4
Intentional drug misuse	3
Insomnia*	2
Rash*	2
Psychomotor hyperactivity*	2

* The top 5 most frequent events included events reported 2 or more times, of which there were 3 adverse events reported twice.

One pediatric post-marketing report of IRIS was identified. The patient was a 16 year old male with AIDS encephalopathy and spastic cerebral paresis who was placed on therapy with raltegravir 400 mg tablet, half a tablet, twice a day for the treatment of HIV infection stage C3 (multiresistant virus). Concomitant suspect therapy included enfuvirtide, lamivudine, etravirine, ritonavir and darunavir. Almost one year later, a diagnosis of autoimmune thyroiditis was made. The reporting physician felt that autoimmune thyroiditis was possibly drug-induced by antiretroviral therapy (including raltegravir potassium, enfuvirtide, lamivudine, etravirine, darunavir and ritonavir). He also considered a flare up of endogenous autoimmune thyroiditis in

the context of IRIS as a possible cause. This report of IRIS posed no additional safety concerns about raltegravir.

There was one pediatric post-marketing report of increase in liver enzymes or related clinical hepatic event (hepatic failure). The subject was a 17 year old female patient who developed hepatic failure that was considered life threatening while on therapy with raltegravir 400 mg twice daily for HIV infection. Suspect therapy included atazanavir sulfate 300 mg; ritonavir 100 mg daily; and emtricitabine (+) tenofovir disoproxil fumarate daily. One year later, the patient developed hepatic failure. Therapy with atazanavir sulfate, ritonavir, and emtricitabine (+) tenofovir disoproxil fumarate was discontinued. The patient was started on tenofovir (+) emtricitabine (+) efavirenz, but stayed on raltegravir. After one year, the patient recovered from hepatic failure. This report posed no additional safety concerns about raltegravir.

A total of four pediatric post-marketing reports of use in pregnancy were identified. A review of the cases did not suggest new safety issues with regards to raltegravir exposure during pregnancy in pediatric patients.

In summary, a total of 23 raltegravir pediatric post-marketing adverse experience reports were identified in the WAES database from market introduction (27-Sep-2007) through 31-Dec-2010. The most frequently reported adverse events for raltegravir in the pediatric post-marketing environment are generally consistent with the Company Core Data Sheet (CCDS) for raltegravir and pose no new safety concerns.

8 Postmarket Experience

DAVP and OSE are continuously monitoring post-marketing AEs and reviewing specific events as needed.

Note, a new PMR will be issued with the approval action of the current NDA/sNDA.

9 Appendices

9.1 Literature Review/References

1. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

9.2 Labeling Recommendations

Labeling negotiations with the sponsor are not yet completed. The clinical labeling recommendations completed thus far will be sent to the sponsor. The most relevant pediatric labeling information is included below. Please refer to the US PI and PPI for additional details.

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS)

9.3 Advisory Committee Meeting

There was no Advisory Meeting convened for this application.

9.4 Tables and Attachments

Attachment 1: Pediatric Written Request (PWR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20857

NDA 22-145
IND 69,928

WRITTEN REQUEST – AMENDMENT 2

Merck Sharp & Dohme Corp.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Ave.
P.O. Box 2000, RY33-212
Rahway, New Jersey 07065-0900

Dear Dr. Fromtling:

Reference is made to your April 25, 2006 Proposed Pediatric Study Request submitted to IND 69,928 for raltegravir potassium (formerly MK-0518).

To obtain needed pediatric information on raltegravir potassium, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Types of studies:

Multiple-dose pharmacokinetic, safety, and activity study of raltegravir potassium in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic and safety study of raltegravir potassium in addition to the standard of care in HIV-exposed neonates (born to HIV-infected mothers).

The objective of these studies will be to determine the pharmacokinetic and safety profile of raltegravir potassium across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients and exposed neonates, and evaluate the activity of this dose (or doses) in treatment and/or prophylaxis.

Indication to be studied:

Treatment of HIV infection in pediatric patients and/or prophylaxis of HIV infection in exposed neonates.

Age group in which studies will be performed:

HIV-infected pediatric patients from 1 month to adolescence and HIV-exposed neonates (born to HIV-infected mothers).

Drug Information

Dosage form: Age appropriate-formulation.

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide safety data including gastrointestinal disorders, headache, hepatic toxicity, metabolic disturbances, and any other parameters pertinent to use in the pediatric population.

Safety of raltegravir potassium must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. A minimum of 100 patients with at least 24 weeks safety data is needed.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Birth to < 6 weeks: 8

6 weeks to < 6 months: 6

6 months to < 2 years: 6

2 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters including: C_{max}, C_{min}, T_{max}, and AUC_{0-12}, will be characterized.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of 24 weeks after start of therapy.

Activity

Assessment of changes in plasma HIV RNA levels and in $CD4^+$ cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving raltegravir potassium, particularly from those who experience loss of virologic response.

Labeling that may result from the studies:

Information regarding dosing, safety, and activity in the HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or not Hispanic/ Latino.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before January 5, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency of your intent to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a new drug application (NDA)/supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that raltegravir potassium is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, approvable, not approvable); or
  - the exclusivity determination (i.e., granted or denied).

If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please contact Amalia Himaya, Regulatory Project Manager, at (301) 796-3391 or the Division's main number at (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Edward M. Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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