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Established Name Raltegravir
(Proposed) Trade Name Isentress
Therapeutic Class HIV integrase strand transfer inhibitor
Applicant Merck

Formulation(s) (b) (4) suspension
Dosing Regimen 6 mg/kg PO BID
Indication(s) Treatment of HIV-1 infection
Intended Population(s) Infants (b) (4)
4 weeks (b) (4)

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	4
1.1	Recommendation on Regulatory Action	4
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments	6
2	INTRODUCTION AND REGULATORY BACKGROUND	6
2.1	Product Information	6
2.2	Tables of Currently Available Treatments for Proposed Indications	6
2.3	Availability of Proposed Active Ingredient in the United States	8
2.4	Important Safety Issues With Consideration to Related Drugs.....	8
2.5	Summary of Presubmission Regulatory Activity Related to Submission	8
2.6	Other Relevant Background Information	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
3.1	Submission Quality and Integrity	10
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	10
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	11
4.1	Chemistry Manufacturing and Controls	11
4.2	Clinical Microbiology.....	11
4.3	Preclinical Pharmacology/Toxicology	11
4.4	Clinical Pharmacology	11
4.4.1	Mechanism of Action.....	11
4.4.2	Pharmacodynamics.....	11
4.4.3	Pharmacokinetics.....	12
5	SOURCES OF CLINICAL DATA.....	12
5.2	Review Strategy	13
5.3	Discussion of Individual Studies/Clinical Trials.....	13
6	REVIEW OF EFFICACY	15
	Efficacy Summary.....	15
6.1	Indication	17
6.1.1	Methods	17
6.1.2	Demographics.....	18
	Baseline HIV Characteristics.....	18
	Previous Anti-retroviral Drug Use and Baseline HIV Resistance	20
6.1.3	Subject Disposition	21
6.1.4	Analysis of Primary Endpoint(s).....	22

6.1.5	Analysis of Secondary Endpoints(s).....	24
6.1.6	Other Endpoints	25
6.1.7	Subpopulations	25
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	26
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	27
7	REVIEW OF SAFETY.....	27
	Safety Summary	27
7.1	Methods.....	28
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	28
7.1.2	Categorization of Adverse Events	28
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	28
7.2	Adequacy of Safety Assessments	28
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	29
7.2.2	Explorations for Dose Response.....	29
7.2.3	Special Animal and/or In Vitro Testing	29
7.2.4	Routine Clinical Testing	29
7.2.5	Metabolic, Clearance, and Interaction Workup	29
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	29
7.3	Major Safety Results	30
7.3.1	Deaths.....	30
7.3.3	Dropouts and/or Discontinuations	33
7.3.4	Significant Adverse Events	33
7.3.5	Submission Specific Primary Safety Concerns	35
7.4	Supportive Safety Results	35
7.4.1	Common Adverse Events	35
7.4.2	Laboratory Findings	35
7.4.3	Vital Signs	37
7.4.4	Electrocardiograms (ECGs)	37
7.4.5	Special Safety Studies/Clinical Trials.....	37
7.4.6	Immunogenicity	37
7.4.7	Additional Cohort I – III Long Term Safety Data, Week 0 - 144	37
7.5	Other Safety Explorations.....	38
7.6	Additional Safety Evaluations	38
7.6.1	Human Carcinogenicity	38
7.6.2	Human Reproduction and Pregnancy Data.....	38
7.6.3	Pediatrics and Assessment of Effects on Growth	39
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	39
7.7	Additional Submissions / Safety Issues	39
8	POSTMARKET EXPERIENCE.....	39
9	APPENDICES	40

9.1	Literature Review/References	40
9.2	Labeling Recommendations	40

Table of Tables

Table 1:	Drugs Approved for the treatment of HIV-1 Infections	7
Table 2:	Table of Studies/Clinical Trials	13
Table 3:	Subject Baseline Demographics by Cohort, Final Dose Population	19
Table 4:	Subject Baseline Clinical Characteristics by Cohort, Final Dose Population ...	19
Table 5:	Baseline Antiretroviral Drug Use, and Sensitivity Scoring	20
Table 6:	Subject Disposition	21
Table 7:	Comparison of Raltegravir Exposure (AUC ₁₂ and C ₁₂) and Efficacy in Pediatric Subjects Following Administration of Proposed Dosing Regimen	22
Table 8:	Virologic Outcome at Week 24	23
Table 9:	Efficacy Outcome by Baseline HIV RNA Category	23
Table 10:	Virologic Outcome at Week 48	24
Table 11:	Efficacy Stratified by Response to Therapy	25
Table 12:	Applicant's recommended Raltegravir (b) (4) Suspension Doses by Weight with Target Dose of 6mg/kg BID	27
Table 13:	FDA's Recommended Dose for Isentress (b) (4) Suspension in Pediatric Patients 4 Weeks (b) (4)	27
Table 14:	Nonfatal Serious Adverse Events by Cohort	31
Table 15:	Grade 3 and 4 Adverse Events	32
Table 16:	Summary of Common Clinical Adverse Events by Cohort	35
Table 17:	Grade 3 and 4 Laboratory Events by Preferred Term	36
Table 18:	Hepato-biliary Events by Worst Grade Toxicities	36
Table 19:	Hematological Events by Worst Grade Toxicities	37

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 205786 contains data from the pediatric clinical trial IMPAACT P1066/Merck 022, supporting the use of Isentress® GFS for the treatment of HIV-1 infection in pediatric subjects aged ≥ 4 weeks (b) (4). This reviewer recommends the approval of the NDA, as raltegravir in combination with an optimized anti-retroviral regimen resulted in reduction of HIV-1 RNA viral load in both age groups.

The IMPAACT P1066/Merck 022 study is an Phase I/II multi-center, open-label, non-comparative study containing pharmacokinetic data, as well as safety and efficacy data from pediatric subjects from birth to eighteen years of age. NDA 203045 reviewed safety and efficacy data from Cohorts I – III, which included subjects > 2 years of age to

18 years of age. This submission contains data from Cohorts IV and V, which included 26 HIV-infected infants and toddlers (4 weeks to <2 years) who received the new formulation of oral (b) (4) suspension. The dose of 6mg/kg was chosen to approximate the pharmacokinetics seen in adults and Cohorts I – III; no additional dose finding was performed.

Raltegravir exposure in Cohorts IV and V approximated that seen in Cohorts I-III and adult subjects. Both AUC₁₂ and C₁₂ pharmacokinetic parameters achieved similar or better exposure than the approved dosing for Cohorts I-III. The Clinical Pharmacology team has recommended a simplified dosing regimen that preserves pharmacokinetic exposure.

At Week 24, 39% of subjects had an HIV RNA < 50 copies/mL, and 61% had HIV RNA < 400 copies/mL. By Week 48, 44% of subjects had an HIV RNA < 50 copies/mL, and 61% had HIV RNA < 400 copies/mL. These efficacy numbers were lower than those observed in prior Cohorts, and an additional analysis examining the role of baseline HIV viral load was conducted. It was found that subjects with a baseline viral load < 100,000 copies/mL had efficacy results similar to those seen in Cohorts I – III, which had comparable baseline viral loads. Subjects with a baseline viral load > 100,000 copies/mL demonstrated decreased efficacy at Week 24.

The safety profile for raltegravir in Cohorts IV and V was comparable to that observed in adults and Cohorts I – III. Although adverse events were common and occurred in 96% of subjects, only 39% of subjects reported serious adverse events, with laboratory events making up the majority of serious adverse events. A single patient experienced a serious adverse event that resulted in permanent discontinuation after he developed a grade 3 episode of rash felt to be probably related to the study drug.

Overall, this reviewer recommends approval of the raltegravir (b) (4) suspension in HIV-1 infected children aged ≥ 4 weeks (b) (4). The 6 mg/kg dose appears to produce exposure comparable to that observed in Cohorts I-III and adult subjects. Finally, it should be noted that this trial was not powered for true statistical analysis of safety or efficacy.

1.2 Risk Benefit Assessment

Raltegravir was found to lower HIV viral loads < 400 copies/mL in 61% of subjects when used in conjunction with an optimized anti-retroviral regimen in pediatrics subjects aged ≥ 4 weeks to ≤ 2 years of age, although the effect was diminished at Week 48 in subjects with a baseline viral load > 100,000 copies/mL. It was also found to be safe and well tolerated in pediatric subjects, with no new safety signals appreciated in Cohorts IV and V. Although adverse events were common, only one patient had a serious adverse event attributed to raltegravir. One death was observed during the trial, but it was not felt to be secondary to raltegravir therapy.

The Safety Update Reports (SUR) for Cohorts I – III was also submitted as part of the NDA 205786. No new safety signal was appreciated upon review of the additional safety data. No additional deaths or discontinuations due to raltegravir therapy were observed in the SUR.

Although raltegravir is associated with some risk, the safety events observed in Cohorts IV and V are similar to those seen in adults and Cohorts I – III. Overall, the benefits of raltegravir outweigh potential risks, and this reviewer supports approval of raltegravir for pediatric subjects aged ≥ 4 weeks (b) (4)

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

This submission partly fulfills the Pediatric Written Request and Post Marketing Commitments. The final trial of HIV infected pediatric subjects < 4 weeks of age is ongoing, with a final study report submission date due in 2015.

2 Introduction and Regulatory Background

2.1 Product Information

Raltegravir, or MK-0518, is an HIV integrase strand transfer inhibitor. It inhibits the catalytic activity of HIV integrase, an enzyme required for HIV-1 replication. By inhibiting HIV integrase, Raltegravir prevents the insertion of the HIV genome into the host genome and stops production of new infectious viral particles.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 28 drugs approved for the treatment of HIV-1 infection (excluding fixed dose combinations or different formulations apart from Stribild). Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the approved anti-retroviral drugs.

Table 1: Drugs Approved for the treatment of HIV-1 Infections

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddl)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine	Intelence®
PI	Rilpivirine	Edurant®
	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
	Enfuvirtide (ENF)	Fuzeon®
Fusion/Entry Inhibitor		
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Dolutegravir	Tivicay®
	Raltegravir	Isentress®
Fixed Dosed Combination	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir disoproxil fumarate	Stribild®

2.3 Availability of Proposed Active Ingredient in the United States

Raltegravir was approved in the United States in October 2007, and approved for pediatric use in the United States in December 2011.

2.4 Important Safety Issues With Consideration to Related Drugs

Raltegravir is the first drug in its class to receive approval for use in HIV infection. Since raltegravir's initial approval in 2007, dolutegravir and elvitegravir, as a component of the fixed dose combination Stribild, have also received approval. In general, safety issues include metabolic disorders, immune reconstitution syndrome, rash, liver enzyme elevation, psychiatric disorders and AIDS-defining conditions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is a summary of the history of the Pediatric Development Program of NDA 205786 Isentress (raltegravir) of Merck from Dr. Vargas-Kasambira's summary in NDA 203045:

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 following PREA PMRs were issued:

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

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

Deferred pediatric study under PREA to evaluate the safety and pharmacokinetics of raltegravir in HIV-exposed neonates (born to HIV-infected

mothers). This multiple-dose pharmacokinetic and safety study will evaluate raltegravir in addition to the standard of care in HIV-exposed neonates from ages 0 to 4-6 weeks.

Protocol Submission Date: 12/31/2012

Final Study Report Submission Date: 01/30/2015

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).

On June 30, 2011, the sponsor submitted data aimed at fulfilling the PMR requirement evaluating raltegravir in pediatric subjects 2-18 years or age.

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. The rationale behind the request was that a study involving HIV-infected subjects aged 4 weeks to less than 2 years is currently in progress and involves a new oral granules formulation of raltegravir that is appropriate for administration in this age group (IMPAACT P1066/Merck PN022).



The currently submitted pediatric trial fulfills part of the requirements stated under PREA and PWR. The applicant has submitted pharmacokinetic data for children aged 4 weeks to 2 years of age. Additionally, the current IMPAACT P1066 CSR provides interim long-term follow up data through 144 weeks for children and adolescent, although it is not included in this clinical review.

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.

3.2 Compliance with Good Clinical Practices

According to the applicant, this study 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 or sponsored 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 applicant submitted financial information pertinent to the application. Clinical Investigators were requested to provide information related to their financial interests. Clinical Investigators were certified regarding the absence of financial interests and arrangements following the requirements in 21 CFR 54.4(a)(1). Although the applicant reports that "due diligence" was performed to obtain certification of all investigators, two could not be certified. One investigator left the clinical site and a second did not return the financial disclosure form. A search of internal databases for proprietary or financial interests was performed and did not identify any conflicts. Two investigators were found to have a financial arrangement with Merck. One had performed grant support for rotavirus research from Merck and the second disclosed patent information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues have been identified. Please refer to CMC review by Chunchun Zhang for further details. In summary, CMC concluded that the NDA had provided sufficient manufacturing and stability data for the raltegravir (b) (4) suspension.

4.2 Clinical Microbiology

Please refer to the clinical virology review by Dr. Sung Rhee for complete details. Three subjects had raltegravir resistance data submitted, one of which had a raltegravir resistance-associated primary IN substitution. No changes to the microbiology section of the label were proposed.

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

The pharmacodynamics properties of raltegravir were explored with the initial review and clinical trials. At the time of Study 022 initiation, no clear PK/PD relationships had been established for raltegravir, as all BID doses evaluated in adults (100 BID-600mg

BID) led to similar efficacy outcomes. In addition, the doses were on the plateau of the concentration-response relationships. Thus, the PK goal for the dose finding part of Study 022 was to match the overall exposure (AUC) observed with the approved 400mg BID regimen in adults (GM value 14-25 mcg/hr) and maintain a GM C_{trough} levels above the IC₉₅ of 33 nM.

4.4.3 Pharmacokinetics

Please refer to Clinical Pharmacology review by Dr. Fang Li for complete details. The pediatric exposure goals were designed to simulate those seen with adult exposure in previous clinical trials. It should also be noted that the GFS formulation of raltegravir is not bioequivalent, and thus not directly inter-changeable, to previously approved adult or chewable tabs.

Exposure data in Cohorts IV and V were comparable to data gathered from Cohorts I – III. Cohorts I – III had reported AUC₁₂ of 15.3 – 23.7 μM*hr and C_{12h} of 88.8 to 640.2 nM. Cohort IV reported an AUC₁₂ of 23.3 μM*hr and C_{12h} of 122.3 nM, while Cohort V was shown to have an AUC₁₂ of 28.8 μM*hr and C_{12h} of 144.3 nM. The applicant had aimed to approximate adult AUC₁₂ values ranging from 14 to 45 μM*hr, with C_{12h} greater than 75 nM. C_{max} was found to be significantly higher in Cohorts IV and V; based on the available safety data evaluated, no new types of adverse events were identified.

Generally, the pharmacokinetic data for Cohorts IV and V fell within the goal range for AUC₁₂ and C_{12h}. A simplified dosing regime was recommended by the Clinical Pharmacology team, but resulted in similar pharmacokinetic exposures as the original dosing regimen.

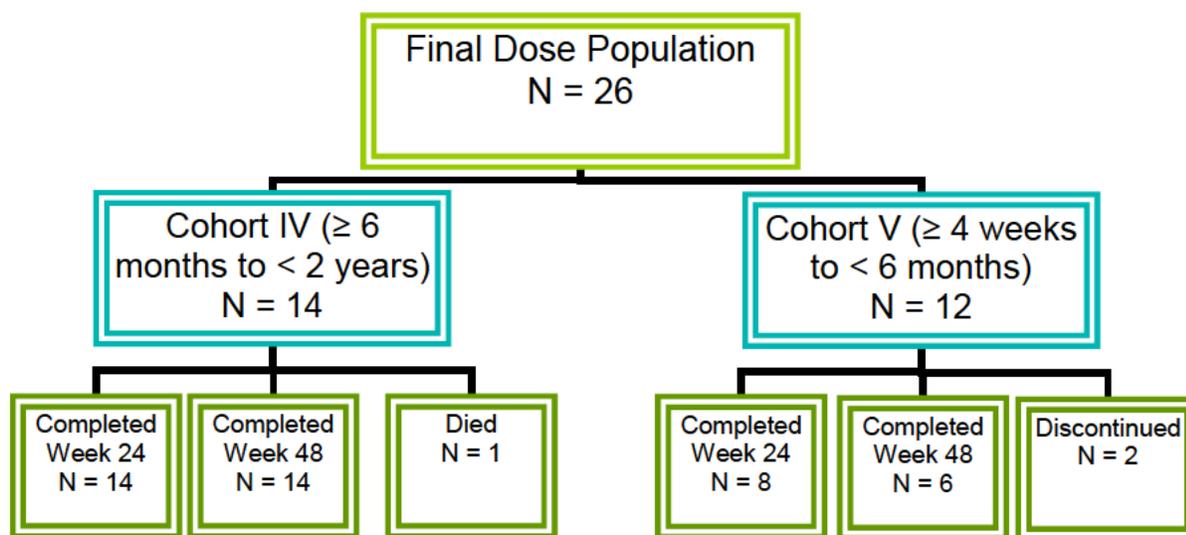
5 Sources of Clinical Data

This submission contains data from IMPAACT P1066 an ongoing Phase I/II multi-center, open-label, non-comparative study containing pharmacokinetic data, as well as Week 24 and 48 safety and efficacy data from 26 HIV-infected infants and toddlers (4 weeks to <2 years). Eleven of fifty-six centers enrolled subjects in five countries for cohorts IV and V. 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.

Table 2: Table of Studies/Clinical Trials

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	26	23	21

Figure 1: Final Dose Population



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.

5.3 Discussion of Individual Studies/Clinical Trials

IMPAACT Trial P1066/Merck 022 is the pivotal trial evaluating the use of raltegravir (both the marketed adult tablet, the chewable tablet formulation and oral granules) in pediatric subjects. The trial was submitted in support of the approval of raltegravir for

treatment of HIV-1 in pediatric subjects ≥ 4 weeks to < 18 years of age in combination with other antiretroviral agents.

IMPAACT P1066 is an ongoing 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 documented HIV-1 infection, with HIV RNA $\geq 1,000$ 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 is administered orally as an adult tablet, chewable tablet, or oral granules for suspension (GFS) in water. This submission reviews the use of raltegravir (b) (4) in children aged ≥ 4 weeks (b) (4). Pediatric subjects were assigned to six cohorts, as described below. This submission reviews subjects in Cohort IV and V.

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

Cohort I: ≥ 12 to < 19 years of age assigned to receive the adult tablet

Cohort IIA: ≥ 6 to < 12 years of age assigned to receive the adult tablet

Cohort IIB: ≥ 6 to < 12 years of age assigned to receive the chewable tablet

Cohort III: ≥ 2 to < 6 years of age assigned to receive chewable tablet

Cohort IV: ≥ 6 months to < 2 years assigned to receive oral granules for suspension

Cohort V: ≥ 4 weeks to < 6 months assigned to receive oral granules for suspension

Raltegravir was administered orally at doses so that the resulting pharmacokinetic profile in pediatric subjects was reasonably similar to that attained in adults at the approved dose of 400 mg twice daily. Subjects received raltegravir GFS at a weight based started dose of ~ 6 mg/kg orally BID. Subjects were required by protocol to have more frequent monitoring of weight in order to ensure appropriate dose adjustments. After 48 weeks, subjects who reached the appropriate age and weight were permitted to change their formulation (e.g. GFS to chewable tablet).

Subjects were enrolled into one of two sequential Stages: I and II. Stage I was the dose-finding period, in which pharmacokinetics, short-term tolerability and safety of raltegravir was studied to permit dose selection for Stage II. Stage I enrollment started with the oldest cohort and progressed to the younger cohorts. If subjects met the PK and safety requirements, the next younger cohort was opened to enrollment. Stage I subjects remained on trial in the Stage I extension. Stage II enrolled additional subjects to assess the long-term safety and efficacy of raltegravir. Cohort IV enrolled subjects into Stage II, but Cohort V did not. The final selected dose of 6mg/kg was identified prior to

enrolling subjects in Cohort V. Eight additional subjects were enrolled into Cohort V to collect additional intensive PK data.

Subjects in Cohort IV may have added raltegravir to an optimized background regimen of ARV, or initiated raltegravir simultaneously with a new background regimen. Cohort V initiated raltegravir simultaneously with a new background regimen. Both Cohorts IV and V must have received therapy to interrupt maternal-infant transmission.

Complete data were available up to Week 24 (primary time point) and Week 48 (secondary time point) for Cohorts IV and V.

The primary objective was (1) to evaluate the short-term safety and tolerability of raltegravir by adding the drug to a stable background therapy or starting raltegravir with a new background regimen, (2) to evaluate the steady state plasma concentration profiles and PK parameters of raltegravir in pediatric subjects and (3) to evaluate the safety and tolerability of raltegravir during the chronic dosing stage in combination with OBT as assessed by review of the accumulated safety data over 24 weeks. 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 C_{max} , C_{12h} , T_{max} , and AUC_{0-12} . For intensive PK evaluation of Stage I subjects in Cohorts IV, blood samples were collected at the following time points: pre-dose, 0.5, 1, 2, 4 and 12 hours post dose. For Cohort V, blood samples were collected at the following time points: pre-dose, 0.5, 1, 3-5, and 8-10 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 subjects receiving raltegravir potassium, particularly from those who experience loss of virologic response.

6 Review of Efficacy

Efficacy Summary

IMPAACT Trial P1066 is a Phase I/II, multi-center, open-label, non-comparative study to compare the effects of raltegravir in combination with optimized background therapy in HIV-1 infected pediatric subjects. Because the trial is single arm, the trial is not a true efficacy study, However,

extrapolation of efficacy for antiretroviral drugs such as raltegravir can be made 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). Thus, one can rely on the pharmacokinetics data to extrapolate efficacy; that is, the goal would be to target the exposure(s) (AUC) that are similar to the observed exposures (AUC) from the approved adult dose(s). Although AUC is the primary pharmacokinetic parameter targeted when selecting pediatric dose(s), C₀ may also be an important pharmacokinetic parameter for some antiretroviral drugs with regards to establishment of exposure-response relationship. In the case of raltegravir both AUC and C₀ were considered when selecting the pediatric once daily dosing. The clinical efficacy (antiviral activity) data obtained from pediatric trials, when available, are used as supportive data.

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), non-nucleoside 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. February 28, 2008 1-134: available at <http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>. for a review of studies and references).

Subjects in IMPAACT Trial P1066 were grouped into five cohorts based on age (≥ 4 weeks to < 6 months, ≥ 6 months to < 2 years, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years and ≥ 12 years to < 19 years). This submission evaluates Cohort IV (≥ 6 months to < 2 years) and Cohort V (≥ 4 weeks to < 6 months) who were given the granules for suspension (GFS) formulation of raltegravir.

Twenty-six subjects were enrolled in the study and received raltegravir. Three subjects in Cohort V were enrolled to provide supplemental pharmacokinetic data and had not yet reached Week 24. Therefore, the efficacy analysis is based on the 23 remaining subjects.

Twenty-three subjects had virologic data at week 24 of therapy including 14 subjects from Cohort IV and 8 subjects from Cohort V. One patient discontinued after one week on therapy due to an adverse reaction

Based on FDA's snapshot analysis, at Week 24, the proportion of subjects with HIV RNA < 50 and < 400 copies/mL were 39% (9/23) and 61% (14/23), respectively. The proportion of subjects considered virologic failures (HIV RNA > 400 copies/mL) was 35% (8/23); in addition, 57% (13/23) had HIV RNA > 50 copies/mL.

At Week 48, the proportion of subjects with HIV RNA <50 and <400 copies/mL were 44% (10/23) and 61% (14/23), respectively. The proportion of subjects considered virologic failures (HIV RNA >400 copies/mL) was 26% (6/23); in addition, 44% (10/23) had HIV RNA >50 copies/mL.

Dr. Vargas-Kasambira reviewed the efficacy data submitted for Cohorts I, II and III. In his review, virologic response at Week 24 was found to be 51/96 (53%) for HIV RNA \leq 50 copies/mL and 65/96 (66%) for HIV RNA \leq 400 copies/mL. At Week 48, Cohorts I, II and III reported HIV RNA less than 50 copies/mL in 65/112 (58.0%) of subjects and HIV RNA less than 400 copies/mL in 83/112 (74.1%) of subjects.

CD4 count increased over the 24-week and 48-week trials. Subgroup analysis examining PSS, baseline HIV RNA category, age, gender and race did not find any significant differences. The sample sizes for the subgroup analysis were very small and limited meaningful analysis.

It was noted that Cohorts IV and V showed decreased efficacy compared to Cohorts I – III. Upon further sub-group analysis, it was found that subjects with a higher baseline viral load demonstrated decreased efficacy, whereas subjects with baseline viral loads similar to those observed in Cohorts I-III had similar efficacy outcomes compared to Cohorts I – III.

6.1 Indication

Raltegravir is currently indicated for the treatment of HIV-1 infection in adults and pediatric patients over two years of age. The applicant seeks to extend the indication to patients above the ages of \geq 4 weeks.

6.1.1 Methods

Primary Efficacy Endpoints included:

- 1) HIV RNA < 400 copies/ml at Week 24/48
- 2) \geq 1 log decline in HIV RNA at Week 24/48
- 3) HIV RNA < 50 copies/ml at Week 24/48

Additional analysis was focused on the steady state plasma concentration profile and pharmacokinetic parameters of raltegravir in infants and children. Concentration-time data was collected to create a population PK model to describe the pediatric exposure of raltegravir and assess drug-drug interactions.

Virologic failure was defined as follows:

1. Never achieved \geq 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 \geq 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 log₁₀ 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.

Although the FDA's efficacy analysis is based on the Snapshot algorithm, the sponsor used the Observed Failure and Non-Completer approaches to handle missing data. The Observed Failure approach considered subjects who prematurely discontinued assigned treatment due to lack of efficacy as failures thereafter. Subjects who prematurely discontinued assigned treatment for reasons other than lack of efficacy were excluded from the analysis. Non-Completers were considered equivalent to failures and consisted of subjects who prematurely discontinued assigned treatment regardless of reasons. Intermittent missing values were assigned as failures unless immediately flanked by two successes.

6.1.2 Demographics

The demographic characteristics of Cohorts IV and V are described in Table 6. 26 subjects were included in the final dose population. The median age was 6.8 months (range 0.98 to 23.1) with a male predominance in both cohorts with 66.7% male and 33.3% female. The majority of subjects were black (85.2%) with white (7.4%), multi-racial (3.7%) or unknown (3.7%) ethnicities making up the remainder of the population.

Baseline HIV Characteristics

Table 3 describes the baseline clinical characteristics of Cohorts IV and V. The CDC HIV classification revealed 37% of subjects were CDC Category A, 11% were CDC Category B, 15% were CDC Category C and 37% were CDC Category N. Of note, patient 8504252 was listed as both category A and N at baseline. The visit with the latest date was used, and as a result patient 8504252 was counted in Category A. 22.5% of subjects were infected with viral subtype Clade B. With regards to Baseline HIV RNA level, most subjects had levels greater than 100,000 (85.2%). In the event two data entries were available for a baseline level, the higher HIV RNA level was used. Median baseline CD4 count was 1398 cells/mm³, and median CD4 percent was 18.6%.

Table 3: Subject Baseline Demographics by Cohort, Final Dose Population

	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N = 26 N (%)
Age (weeks)			
Mean (SD)	54.1(24.4)	14.3 (4.6)	35.7 (27.0)
Median	47	15.5	28
Range	27 - 100	4 - 19	4 - 100
Gender			
Male	9 (64.3)	8 (66.7)	17 (65.4)
Female	5 (35.7)	4 (33.3)	9 (34.6)
Race			
Black/African-American	10 (71.4)	12 (100)	22 (84.6)
White	2 (14.3)	0 (0)	2 (7.7)
American Indian	0 (0)	0 (0)	0 (0)
Multi-racial	1 (7.1)	0 (0)	1 (3.9)
Unknown	1 (7.1)	0 (0)	1 (3.9)
Ethnicity			
Hispanic/Latino	5 (35.7)	0 (0)	5 (19.2)
Not Hispanic/Latino	3 (21.4)	8 (66.7)	11 (42.3)
Unknown	6 (42.9)	4 (33.3)	10 (38.5)

Source: Patient.xpt, case.xpt

The higher viral loads observed in these cohorts likely reflects the younger age of the patient and their relative inexperience with ARVs. Cohorts I, II and III were observed to have a lower viral load, consistent with their history of HIV therapy. The CD4 percentage provides evidence of viral suppression present in all age groups.

Table 4: Subject Baseline Clinical Characteristics by Cohort, Final Dose Population

	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
CDC HIV Clinical Classification			
A	6 (42.3)	4 (33.3)	10 (38.5)
B	2 (14.3)	1(8.33)	3 (11.5)
C	3 (21.4)	0 (0)	3 (11.5)
N	3 (21.4)	7 (58.3)	10 (38.5)
Viral Subtype			
Clade B	4 (28.6)	2 (16.7)	6 (23.1)
Non-clade B[†]	9 (64.3)	6 (50)	15 (57.7)
Unknown	1 (7.1)	4(33.3)	5 (19.2/)
Baseline Plasma HIV RNA (copies/mL)			
0 to ≤ 4,000	1 (7.1)	0 (0)	1 (3.8)
> 4,000 to ≤ 50,000	1 (7.1)	2 (16.7)	3 (11.5)
> 50,000 to ≤ 100,000	3 (21.4)	1 (8.3)	4 (15.4)
> 100,000	9 (64.2)	9 (75)	18 (69.2)

	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Baseline CD4 Count (cells/mm³)			
Mean (SD)	1647.5 (965.7)	1359.6 (1003.8)	1514.6 (974.5)
Median	1684	1231.5	1400
Range	286 – 3345	131 - 3648	131 - 3648
Baseline CD4 percentage			
Mean (SD)	22.6 (8.1)	18.4 (11.5)	20.7 (9.9)
Median	24	17.2	18.6
Range	7.7 – 34.2	3.3 – 39.3	3.3 – 39.3

N = Number of subjects in each cohort.

n (%) = Number (percent) of subjects in each subcategory.

†Non-Clade B subtypes reported include: A, C and F1.

Source pe0013.xpt, pe0014.xpt, HIVRSST.xpt

Previous Anti-retroviral Drug Use and Baseline HIV Resistance

All subjects had been exposed to prior ARV therapy. Given that the patient population was recruited from pediatric subjects who had been exposed to ARV for the prevention of mother-to-child transmission and/or had been started on combination ARV after birth, this finding was not surprising. Only two subjects in Cohort IV (14.3%) had exposure to three or more ARVs. This would be expected, as the youngest subjects were enrolled in Cohort V.

The Genotypic Sensitivity Score (GSS) and Phenotypic Sensitivity Score (PSS) are the number of ARVs in a subject's OBT to which the viral isolate was sensitive, based upon initial resistance testing. 77% of all subjects had PSS and GSS scores of 2 or greater, indicating moderate ARV sensitivity at baseline. 19% of subjects did not have baseline data available and one patient in Cohort V has a GSS and PSS score of 1. This patient was likely infected with a resistant strain of virus during mother-to-child transmission at birth.

Table 5: Baseline Antiretroviral Drug Use, and Sensitivity Scoring

	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Number of ARV Classes Previously Used			
0	0 (0)	0 (0)	0 (0)
1	8 (57.1)	10 (83.3)	18 (69.2)
2	4 (28.6)	2 (16.7)	6 (23.1)
≥ 3	2 (14.3)	0 (0)	2 (7.69)
Subjects with Prior NNRTI Use	8 (57.1)	11 (91.7)	19 (73.1)
Subjects with Prior PI Use	5 (35.7)	0 (0)	5 (11.5)

	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Phenotypic Sensitivity Score (PSS) ‡			
0	0 (0)	0 (0)	0 (0)
1	0 (0)	1 (8.3)	1 (3.9)
2	2 (14.2)	5 (41.7)	7 (26.9)
≥ 3	9 (64.3)	4 (33.3)	13 (50)
Missing	3 (21.4)	2 (16.7)	5 (19.2)
Genotypic Sensitivity Score (GSS) ‡			
0	0 (0)	0 (0)	0 (0)
1	0 (0)	1 (8.3)	1 (3.9)
2	3 (21.4)	5 (41.7)	8 (30.8)
≥ 3	10 (71.4)	2 (16.7)	12 (46.2)
Missing	1 (7.1)	4 (33.3)	5 (19.2)

Source: BSL45.xpt

N = Number of subjects in each cohort.

n (%) = Number (percent) of subjects 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

Twenty-seven subjects were initially enrolled in the study. One patient from Cohort IV discontinued prior to receiving any study medication. The remaining 26 subjects comprised the Final Dose Population. One subject in Cohort V withdrew due to transportation limitations. One subject in Cohort IV died during the study, and one subject in Cohort V discontinued due to an adverse reaction felt to be secondary to study medication.

Table 6: Subject Disposition

	Cohort IV N=15 n (%)	Cohort V N=12 n (%)	Total N=27 n (%)
Off Trial Drug	2 (13.3)	2 (16.7)	4 (14.8)
Protocol-Defined Clinical Event	0 (0)	1 (8.3)	1 (3.7)
Guardian consent withdrawn	1 (6.7)	0(0)	1(3.7)
Not able to attend clinic	0 (0)	1 (8.3)	1 (3.7)
Non-adherent	0 (0)	0(0)	0 (0)
Death	1 (6.7)	0(0)	1 (3.7)
Off Trial	2 (13.3)	1(8.3)	3 (11.1)
Subject/parent unable to reach clinic	0 (0)	1(8.3)	1 (3.7)
Subject/parent withdrew consent prior to trial completion	1 (6.7)	0(0)	1 (6.7)
Death	1 (6.7)	0(0)	1 (3.7)

6.1.4 Analysis of Primary Endpoint(s)

The evaluation of pharmacokinetic data was also a primary endpoint. As discussed above, the goal was to target the exposure(s) (AUC) in pediatric subjects that are similar to the observed exposures (AUC) from the approved adult dose(s). Although AUC is the primary pharmacokinetic parameter targeted when selecting pediatric dose(s), C_{trough} was also an important pharmacokinetic parameter with regards to establishment of exposure-response relationship. Thus, the PK data was relied upon to extrapolate efficacy; the clinical efficacy (antiviral activity) data obtained from the trial is used as supportive data.

Please refer to Dr. Fang Li's review for a complete analysis of PK data. Briefly, the raltegravir GFS formulation was not found to be bioequivalent to the adult or chewable tabs, with increased rate of absorption observed in the GFS formulation. However, the clearance of raltegravir was not found to be affected. The observed exposures of AUC_{12} and $C_{12\text{hr}}$ were similar to those observed in adults and Cohorts I – III, as seen in the table below.

Table 7: Comparison of Raltegravir Exposure (AUC_{12} and C_{12}) and Efficacy in Pediatric Subjects Following Administration of Proposed Dosing Regimen

	I (12y to 18y)	IIA (6y to 12y)	IIB (6y to 12y, 6mg/kg)	III (2y to 6y) 6 mg/kg	IV (6m to 2y) 6 mg/kg	V (4wk-6m) 6 mg/kg	Adult (400mg BID)
N	21	14	10	12	8	11	
AUC_{12} ($\mu\text{M}\cdot\text{hr}$)	18.2	15.3	23.7	21.3	23.3	28.8	14.3
C_{12}(nM)	640.2	487	177.1	88.8	122.3	144.3	142

Table adapted from Dr. Fang Li's Clinical Pharmacology Review.

Primary Efficacy Endpoints included the proportion of subjects with (1) HIV RNA < 400 copies/ml at Week 24, (2) HIV RNA < 50 copies/ml at Week 24 and (3) ≥ 1 log decline in HIV RNA at Week 24. Baseline changes in HIV RNA, CD4 count and CD4 percentage were also among the primary efficacy endpoints.

Using the FDA's snapshot algorithm, the proportion of subjects with HIV RNA <50 and <400 copies/mL at Week 24 were 39% (9/23) and 61% (14/23), respectively. The proportion of subjects considered virologic failures (HIV RNA >400 copies/mL) was 35% (8/23); in addition, 57% (13/23) had HIV RNA >50 copies/mL. The applicant determined that 42.9% of subjects had an HIV RNA < 50 copies/ml and 63.6% of subjects had an HIV RNA <400 copies/ml at Week 24; virologic data was missing for one subject at Week 24.

Table 8: Virologic Outcome at Week 24

Virologic Success n, (%)	HIV RNA < 50 copies/mL: 9/23 (39.1)	HIV RNA < 400 copies/mL: 14/23 (60.9)
Virologic Failures n, (%)	HIV RNA ≥ 50 copies/mL: 13/23 (56.5)	HIV RNA ≥ 400 copies/mL: 8/23 (34.8)
No Virologic Data at 24 Week Window		
Discontinued trial/trial drug due to AE or death*	1/23 (4.3)	
Discontinued trial/trial drug for Other Reasons	0/23	
Missing data during window but on study	0/23	

Source: HIVRST.xpt, LRNAFIN.xpt

The efficacy rate of raltegravir was somewhat lower in these two youngest age cohorts compared to the older age cohorts. The analysis of subjects in Cohorts I – III had reported 53.1% of subjects with HIV RNA <50 copies/ml and 65.6% of subjects with HIV RNA < 400 copies at 24 weeks. Failure rates (HIV RNA >400 copies/mL) between prior cohorts and the current analysis were similar. Overall, 35% and 33% had HIV RNA > 400 copies/ml in Cohorts IV-V and Cohorts I-III, respectively.

Several additional analyses were conducted to identify a factor contributing to the lower efficacy rate in the younger age cohorts. Among the factors considered were lower exposures and baseline characteristics. As discussed above, the exposures were considered adequate. However, baseline HIV RNA may have influenced the efficacy outcome. Subjects were stratified by baseline HIV RNA ≤100,000 copies/mL and >100,000 copies/mL. Compared to the older age groups, the HIV RNA at baseline was significantly higher in Cohorts V and VI. The response appears greater in subjects with baseline HIV RNA ≤100,000 copies/mL; however, the small sample size may confound results. As summarized in the table below, the proportion of subjects with HIV RNA <50 were 63% (5/8) and 26% (4/15), for subjects with baseline HIV RNA <100,000 copies/mL and >100,000 copies/mL, respectively.

Table 9: Efficacy Outcome by Baseline HIV RNA Category

Virologic Parameter at Week 24	≤ 100,000 copies/mL N=8 n (%)	> 100,000 copies/mL N=15 n (%)
HIV RNA < 50 copies/mL	5/8 (62.5)	4/15 (26.7)
HIV RNA < 400 copies/mL	6/8 (75)	8/15 (53.3)
Virologic Parameter at Week 48	≤ 100,000 copies/mL N=8 n (%)	> 100,000 copies/mL N=15 n (%)
HIV RNA < 50 copies/mL	4/8 (50)	5/15 (33.3)

Virologic Parameter at Week 24	≤ 100,000 copies/mL N=8 n (%)	> 100,000 copies/mL N=15 n (%)
HIV RNA < 400 copies/mL	6/8 (75)	8/15 (53.3)

Source: HIVRSST.xpt, LRNAFIN.xpt

The mean change from baseline in CD4 was 483.6 at Week 24, while the mean change in CD4 percent was 6.7. The applicant reported a mean change in CD4 of 500.1 and a change in CD4 percent of 7.5.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints included the proportion of subjects with efficacy outcomes at Week 48.

At Week 48, 44% of subjects reported an HIV RNA < 50 copies/ml, and 61% reported HIV RNA < 400 copies/ml. The applicant also found the week 48 HIV RNA < 50 copies/ml to be 53%, and the HIV RNA < 400 copies/ml rate to be 70%. Virologic data was missing for three subjects, one of which discontinued due to an adverse reaction, and a second discontinuing due to transportation problems. One other patient was on study drug, but out of the country when his 48 week labs were due.

Table 10: Virologic Outcome at Week 48

Virologic Success n, (%)	HIV RNA < 50 copies/mL: 10/23 (43.5%)	HIV RNA < 400 copies/mL: 14/23 (60.8%)
Virologic Failures n, (%)	HIV RNA ≥ 50 copies/mL: 10/23 (43.5%)	HIV RNA ≥ 400 copies/mL: 6/23 (26.1%)
No Virologic Data at 48 Week Window		
Discontinued trial/trial drug due to AE or death*	1/23 (4.3)	
Discontinued trial/trial drug for Other Reasons	1/23 (4.3)	
Missing data during window but on study	1/23 (4.3)	

Source: HIVRSST.xpt, LRNAFIN.xpt

The mean change from baseline in CD4 was 598.5 at Week 48, while the mean change in CD4 percent was 7.7. The applicant reported a mean change in CD4 of 492.0 and a change in CD4 percent of 7.8.

6.1.6 Other Endpoints

The tertiary efficacy endpoint included the analysis of efficacy for subjects treated more than 48 weeks. As of August 8, 2013, only four subjects in Cohorts IV and V had 96 week data submitted. No further analysis was performed.

6.1.7 Subpopulations

Analysis by PSS score

The small sample size made subgroup analysis via PSS score largely meaningless. Only patient 2020159 had a PSS less than two, indicating a more resistant strain of virus. Review of the baseline viral load data shows that patient 2020159 had a viral load of 4497 copies/ml on study entry. Further stratification by PSS category <2 and ≥2 was not performed due to the small sample size. It would be expected that subjects with a more sensitive strain of virus would show a trend towards more virologic success. If more data was available, it may be possible to see such a trend. No further conclusions can be drawn at this time.

Analysis of non-responders

Overall, of subjects that were considered virologic failures, only a small percentage were failures due to virologic rebound. Subjects were considered to rebound if they had two consecutive viral loads above the success parameter. At week 24, only two subjects were considered not-suppressed due to rebound at the 50 copies/ml parameter. At week 48, four subjects did not meet the HIV RNA <50 copies/mL cut off due to rebound and 3 subjects were virologic failures due to rebound at the 400 copies/ml parameter. Table 11 summaries all rebounds by week and virologic success parameter.

Table 11: Efficacy Stratified by Response to Therapy

Virologic Parameter at Week 24	Never Suppressed N= 23 N (%)	Rebound N= 23 N (%)
HIV RNA ≥ 50 copies/mL	11/23 (47.8)	2/23 (8.7)
HIV RNA ≥ 400 copies/mL	8/23 (34.8)	0/23 (0)
No Virologic Data at 24 Week Window		
Discontinued trial/trial drug due to AE or death*	1/23 (4.3)	
Discontinued trial/trial drug for Other Reasons	0/23	
Missing data during window but on study	0/23	
Virologic Parameter at Week 48	Never Suppressed N= 23 N (%)	Rebound N= 23 N (%)
HIV RNA ≥ 50 copies/mL	6/23 (26.1)	4/23 (17.4)

HIV RNA \geq 400 copies/mL	3/23 (13.0)	3/23 (13.0)
No Virologic Data at 48 Week Window		
Discontinued trial/trial drug due to AE or death*	1/23 (4.3)	
Discontinued trial/trial drug for Other Reasons	1/23 (4.3)	
Missing data during window but on study	1/23 (4.3)	

Source: HIVRSST.xpt, LRNAFIN.xpt

Analysis by Age, Gender and Race

The efficacy of raltegravir was analyzed by age using the cohort-based age stratifications (\geq 6 months to $<$ 2 years and \geq 4 weeks to $<$ 6 months). The small size precludes meaningful analysis, but no trend is apparent. Prior analysis of cohorts I, II and III also did not find any changes in efficacy with age group.

The efficacy of raltegravir was also analyzed by gender. Again, the small sample size challenged significant analysis. No meaningful trends were identified between male and female subjects at week 24 or 48. Previous subgroup analysis of Cohorts I, II and III had suggested greater efficacy in male subjects. While male subjects did have higher efficacy responses at Week 24, by Week 48 any difference had resolved. It seems unlikely that the mechanism of action of raltegravir would significantly differ between male and female subjects. Any observed difference is likely a result of the small sample size.

Black or African-American subjects made up the majority of subjects enrolled in Cohorts IV and V. As a result, any further subgroup analysis cannot be performed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This study was designed to identify the pediatric dosing of raltegravir comparable to the final adult dose of 400mg BID. Stage I of the trial was designed to identify the appropriate dose via intensive PK study, while Stage II monitored long-term safety and antiretroviral activity.

Table 12 demonstrates the Applicant's recommended dose of raltegravir by weight for pediatric subjects taking the GFS formulation. However, revising to the dosing recommendations was made by the team to simplify and streamline the dosing weight bands for subjects. Please refer to Table 13 for the FDA recommended dosing chart. The revised dosing chart maintains the 6mg/kg dosing goal, but allows individual dosing to range from 80-125% of the goal. Most subjects will receive an identical dose, although some may receive a higher dose, up to 7.5mg/kg. Subjects who received higher doses during the clinical trial did not experience increased adverse events. Therefore, with the revised dosing regimen, the efficacy of raltegravir will be maintained without significant changes to exposure-response outcomes.

Table 12: Applicant's recommended Raltegravir (b) (4) Suspension Doses by Weight with Target Dose of 6mg/kg BID

Weight Range in	Raltegravir Dose in	Volume of Suspension to Administer
(b) (4)		
Final suspension concentration is 20 mg/mL.		

Taken from p022v1 clinical study.

Table 13: FDA's Recommended Dose for Isentress (b) (4) Suspension in Pediatric Patients 4 Weeks (b) (4)

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

Source: Dr. Fang Li Clinical Pharmacology Review*
 The weight-based dosing recommendation for (b) (4) suspension is based on approximately 6 mg/kg/dose twice daily.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The treatment effect was persistent to week 48 in Cohorts IV and V, as demonstrated by the virologic response and CD4 counts. Please see sections 6.1.4 and 6.1.5 for details. (b) (4)

7 Review of Safety

Safety Summary

Raltegravir was found to be safe and tolerable in children aged ≥ 4 weeks to < 2 years. In general, the number of serious adverse events was low, with all events only occurring in only one or two subjects. Previous safety analysis in Cohorts I to III had also found a low occurrence of serious adverse events. The proportion of subjects in Cohorts IV and V with a serious adverse is higher than that observed in Cohorts I to III, likely due to the small sample size of Cohorts IV and V. The rates of adverse events of interest including metabolic disorders, IRIS, rash, liver enzyme elevation, and AIDS-defining conditions

were also very low. The incidence of psychiatric disorders could not be assessed due to the age of the enrolled cohorts.

7.1 Methods

As previously agreed with the Division, an Integrated Summary of Safety (ISS) was not provided for this submission. Electronic datasets of safety data provided by the sponsor was analyzed using JMP Statistical Discovery Software and Microsoft Excel.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All data used to evaluate the safety of raltegravir in children ≥ 4 weeks to < 2 years was provided by the pivotal clinical trial P1066/Merck 022. The safety of raltegravir in adults and children > 2 years of age had previously been established and raltegravir has been marketed since 2007 for the treatment of HIV. The primary objective of the trial was to establish the safety of raltegravir over a 48-week time period. Safety was initially assessed after 24 weeks of raltegravir therapy, followed by another 24 weeks of therapy to assess for long-term or chronic adverse events.

7.1.2 Categorization of Adverse Events

In addition to the overall safety profile, adverse events were also categorized as serious adverse events (SAE), adverse events grade 3 or greater, events considered related to study drug, events leading to permanent discontinuation of study drug and events leading to death. Laboratory events also considered separately from clinical adverse events. All safety events were submitted by SAS transport file and analyzed in JMP or Excel software. Events were graded by the investigator based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experience (DAIDS criteria). A drug-related adverse event was one the investigator considered possibly, probably or definitely related to raltegravir; causality was generally not provided for events grade 2 or less.

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 safety assessments were considered sufficient, as raltegravir is already approved in adults and children > 2 years of age.

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

At the time the data was submitted, most subjects had completed 48 weeks of therapy with raltegravir. Four additional subjects were recruited into Cohort V to provide additional intensive PK data, but at this time there is less than 24 weeks of safety and efficacy data available for those subjects.

Please see Table 3 and 4 for patient demographic information.

7.2.2 Explorations for Dose Response

Raltegravir dosing was based upon weight and age. All subjects in Cohorts IV and V received the granules for suspension formulation of the drug. Subjects received 6mg/kg of raltegravir, provided in a 20mg/ml suspension. Subjects who reached the appropriate age and weight could be transitioned to the chewable formulation and study physicians were instructed to transition the subjects to the chewable tablet by age 3. At the time the data was submitted, no subjects had yet transitioned to the chewable tablet. The administered doses ranged from 20mg to 80mg BID with weight-based dosing ranging from 5.102 to 7.143 mg/kg.

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 occurred at screening and trial entry, Week 0, Safety Visit (for Stage I subjects increased to Stage II dose) Week 1 (Intensive PK), 4, 8, 12, 24, 36, and 48, 14-days post therapy, and if a patient discontinued early. All subjects had laboratory data and a clinical evaluation at these visits.

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

No deaths occurred between Week 0 and Week 48 of therapy. A single death occurred during the trial. Patient 2020164, a 27-month old black male died at week 59 on raltegravir therapy. The cause of death was gastroenteritis, and was not attributed to raltegravir by the applicant.

Narrative: Patient 2020164 was a 27-month old black male with a history of pulmonary tuberculosis, HIV encephalopathy and epilepsy. He was enrolled on raltegravir therapy on September 28, 2011. He had also experienced serious adverse events including dyspnea, hypoglycemia and increased bilirubin levels during raltegravir therapy. On day (b) (6) of the study, the patient developed diarrhea and vomiting. He was assessed at a local clinic and given oral rehydration therapy. He was discharged home to Mom to continue oral rehydration. On day (b) (6), he had large volume emesis. Per report, the Mother did not administer any additional fluids. She awoke at (b) (6) to find the patient deceased, with cause of death declared to be gastroenteritis.

The patient's last recorded HIV RNA at week 48 was 24427, and at week 36 was 854. The last two CD4 counts at weeks 48 and 36 were 1229 and 2838 respectively. Given that clinical data for patient 2020164 is limited and does not include supporting laboratory data prior to his death, it is difficult to definitively determine the role of raltegravir in this patient's death. His prior serious adverse reactions while on raltegravir included hypoglycemia, which also could have contributed to his death if he was predisposed to this reaction while on raltegravir. At this time, it cannot be determined what role, if any, raltegravir had in this patient's death.

7.3.2 Nonfatal Serious Adverse Events

A total of 16 non-fatal serious adverse events in 9 subjects were reported for Cohorts IV and V, representing 39% of the total study population. No single category of events accounted for the majority of episodes. Nine events were laboratory events. The majority of events occurred within Cohort IV, with only two subjects in Cohort V reporting serious adverse events. All events occurred at a frequency greater than 2%, due to the small sample size. Only hypocapnia, dyspnea and neutropenia occurred in >5%. An episode of grade 4 hypokalemia was reported by the study sponsor, but could not be located within the safety data submitted.

The small sample size and limited number of events precludes meaningful comparison to Cohorts I to III. Cohorts I to III noted a predominance of infectious SAEs, and did not observe any episodes of respiratory distress. The proportion of subjects in Cohorts IV and V (35%) who experienced a SAE is greater than that seen in Cohorts I to III (14%). Table 14 summarizes the SAEs by patient cohort.

Table 14: Nonfatal Serious Adverse Events by Cohort

Preferred Term	Cohort IV N= 14 n (%)	Cohort V N= 12 n (%)	Total N=26 n (%)
Laboratory Serious Adverse Events			
Anemia	1 (7.1)	0	1 (3.8)
Decreased Bicarbonate	1 (7.1)	1 (8.3)	2 (7.7)
Elevated Lipase	1 (7.1)	0	1 (3.8)
Neutropenia	2 (14.3)	0	2 (7.7)
Hypoglycemia	1 (7.1)	0	1 (3.8)
Elevated Bilirubin	1 (7.1)	0	1 (3.8)
Clinical Serious Adverse Events			
Dyspnea	2 (14.3)	0	2 (7.7)
Pneumonia	0	1 (8.3)	1 (3.8)
Shock	0	1 (8.3)	1 (3.8)
Rash	0	1 (8.3)	1 (3.8)
Wheezing	1 (7.1)	0	1(3.8)
Abdominal Abscess	1 (7.1)	0	1 (3.8)

Source: eae.xpt, events.xpt

Among the SAEs, events of particular interest included one episode of anemia, elevated lipase and elevated bilirubin. The episode of grade 4 anemia occurred in a 12 month old black male (8504486) during week 13. It was considered by the sponsor to be not related to raltegravir treatment. Raltegravir was not held or discontinued and the anemia resolved without further incident. The patient was also receiving zidovudine, lamivudine and nevirapine as his optimized ARV regime.

Patient 801525, a 17 month old black male, experienced a grade 4 episode of elevated lipase. The event occurred on day 11 of raltegravir, and was reviewed by a Safety Monitoring Committee. The committee found that the patient was also infected with CMV and EBV and felt that the lipase elevation was not related to raltegravir. The study drug was temporarily held, and ultimately was not discontinued. The patient recovered without further incident.

The episode of grade 3 elevated bilirubin occurred in a 20 month old black male (2020164) on Week 12 of study drug. The patient was not jaundiced and had no change in his hepatosplenomegaly on exam. Raltegravir was not held or discontinued. The event was not considered related to study medication and ultimately resolved without

intervention. The patient also received abacavir, lamivudine and kaletra as his optimized background ARV regime.

Grade 3 and 4 Clinical Adverse Events

25 grade 3 or 4 clinical adverse events occurred in ten subjects (38%) in Cohorts IV and V between week 0 and 48. Six subjects (43%) in Cohort IV and four subjects (33%) in Cohort V experienced a grade 3 or 4 adverse event. This is significantly higher than Cohorts I to III, where only 13.5% of subjects experienced a grade 3 or 4 AE from week 0 to 24. The longer time interval may account for some of the increase in rate.

The most common AEs occurred in Blood and Lymphatic System disorders (3 subjects, 12%) and Investigations (8 subjects, 31%). Cohorts I to III had reported the majority of grade 3 or 4 events in the Infections and Infestations category. The limited sample size may account for these differences.

Table 15: Grade 3 and 4 Adverse Events

Preferred Term	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Laboratory Adverse Events			
Increased lipase	1 (7.1)	0	1 (3.8)
Increased ALT	1 (7.1)	0	1 (3.8)
Anemia	2 (14.2)	0	2 (7.7)
Bicarbonate decreased	1 (7.1)	1 (8.3)	2 (7.7)
Increased bilirubin	1 (7.1)	0	1 (3.8)
Hyperkalemia	0	1 (8.3)	1 (3.8)
Hypoglycemia	1 (7.1)	0	1 (3.8)
Neutropenia	2 (14.2)	0	2 (7.7)
Clinical Adverse Events			
Dyspnea	1 (7.1)	0	1 (3.8)
Gastroenteritis	0	1 (8.3)	1 (3.8)
Hypoacusis	1 (7.1)	0	1 (3.8)
Hypovolemic Shock	0	1 (8.3)	1 (3.8)
Abdominal Abscess	1 (7.1)	0	1 (3.8)
Rash	0	1 (8.3)	1 (3.8)
Muscle Spasticity	1 (7.1)	0	1 (3.8)
Diarrhea	1 (7.1)	1 (8.3)	2 (7.7)
Pneumonia	0	1 (8.3)	1 (3.8)
Vision abnormal neonate	1 (7.1)	0	1 (3.8)

Preferred Term	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Vomiting	1 (7.1)	0	1 (3.8)
Wheezing	1 (7.1)	0	1 (3.8)

Source: eae.xpt, events.xpt

For narratives describing the episodes of elevated lipase, bilirubin and anemia, please refer to section 7.3.2: Non-fatal serious adverse events. There was one additional event of interest among the Grade 3 and 4 adverse events. Patient 8504252, a one year old white male, experienced a grade 3 elevation in ALT at week 0. No further details are provided.

No cases that fulfilled criteria for Hy’s law of drug-induced liver injury were appreciated.

7.3.3 Dropouts and/or Discontinuations

A single patient experienced a serious adverse event that resulted in permanent discontinuation of raltegravir within one week of starting therapy. Patient 1270100, a 17-week old black male, experienced a grade 3 erythematous rash on day 6 of therapy felt to be probably related to raltegravir therapy.

Narrative: Patient 1270100 was a 17 week old black male with a history of cough treated with amoxicillin/clavulanate one week prior to starting raltegravir. On day 6, he developed cough and shortness of breath and was admitted for IV antibiotics for potential pneumonia. He was started on cefotaxime and vancomycin in addition to his ARVs, including raltegravir. On day 7, he developed a new generalized erythematous rash that progressively worsened throughout his admission. On day 8, raltegravir was permanently discontinued, with subsequent improvement of the rash on day 9 and complete resolution by day 14. He was ultimately diagnosed with *Pneumocystis jiroveci* pneumonia, and possible sepsis. His rash was felt to be probably related to raltegravir.

One patient in Cohort V permanently discontinued raltegravir therapy due to transportation difficulties after the family moved. No SAEs or grade 3 or 4 adverse events were recorded for this patient.

7.3.4 Significant Adverse Events

Adverse events of particular interest included immune reconstitution syndrome (IRIS), rash, AST/ALT elevations, and AIDS-defining conditions. Psychiatric disorders were examined as events of interest in adults and Cohorts I to III, however, no psychiatric adverse events were noted for Cohorts IV and V, likely secondary to their age <2 years. No new safety signals were appreciated in Cohorts IV and V.

Immune Reconstitution Syndrome (IRIS)

One patient developed immune reconstitution syndrome (IRIS) while enrolled on raltegravir therapy. Patient 2020171 was a four month old black male who was reported to developed IRIS four weeks after starting ARV therapy. He was reported to have IRIS secondary to *Mycobacterium bovis* (BCG strain) and reportedly recovered by week 24 without interruption of study treatment. The patient ultimately left the trial at week 36 when his family moved and they were no longer able to attend clinic.

Rash

Rash was noted in 20(77%) participants during the trial, including 15 cases of rash, 1 case of rash erythematous, 1 case of vulvovaginal rash, 5 cases of rash generalized, 2 cases of erythema, 2 cases of eczema, 1 drug eruption, 3 cases of diaper dermatitis, 3 cases of atopic dermatitis and two cases of allergic dermatitis. There was overlap between cases of rash with some subjects having multiple types of rash. All subjects were on multiple ARVs during the trial. The episode of drug eruption was felt to be probably secondary to raltegravir use and was scored as a Grade 3 event with subsequent raltegravir discontinuation. One episode of allergic dermatitis occurred in the same patient. Please see section 7.3.3 for the full narrative. The second episode of allergic dermatitis occurred in patient 8501806 and was described as an allergic rash on the left side of the abdomen due to tape being applied to the patient's g-tube. All other episodes of rash were considered mild or moderate, scoring grade 1 or 2 on the DAIDS scale.

AST/ALT Elevations

Many subjects were noted to have AST(13 subjects, 50%) or ALT elevations (13 subjects, 50%), but few were Grade 3 or 4 events. 11 subjects experienced both an AST and an ALT at some point during the trial. Only one episode of ALT elevation qualified as a grade 3 adverse event (7.1%). Although the sponsor study reports describes a grade 3 AST elevation, the only AST/ALT abnormality to be scored as a grade 3 occurred in patient 8504252 who experienced a ALT elevation. The study drug was not discontinued and the sponsor did not consider this event to be secondary to raltegravir. The maximum ALT value was 217 U/L and occurred on Week 0. Repeat ALT labs demonstrated resolution of the elevated ALT.

AIDS-Defining Conditions (ADC)

There were several AIDS-Defining Conditions that occurred over the course of the study. The reported events included four cases of HIV encephalopathy, one case of CMV pancreatitis, one case of esophageal candidiasis, one case of *Pneumocystis jiroveci* pneumonia and one case of pulmonary tuberculosis. All episodes occurred within week 0 and 48 of therapy.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4 ‘Significant Adverse Events’ above.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events occurred in 25 (96%) of study participants. The most common AEs were rash (81%), cough (77%) and rhinorrhea (65%). Table 16 lists the common adverse events that were present in >15% (4 subjects). These common adverse events seen in Cohorts I to III were also cough (41%), pyrexia (32%) and rhinorrhea (26%). The proportional differences are likely due to the sample size difference. Most adverse events were categorized as mild or moderate, with very few events classified as serious or ≥ Grade 3 events.

Table 16: Summary of Common Clinical Adverse Events by Cohort

Adverse Events Preferred Term	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
AIDS Encephalopathy	3 (21.4)	0	3 (11.5)
Cough	10 (71.4)	10 (83.3)	20 (76.9)
Decreased Appetite	2 (14.3)	2 (16.7)	4 (15.4)
Diarrhea	8 (57.1)	6 (50)	14 (53.8)
Failure to Thrive	5 (35.7)	2 (16.7)	8 (30.8)
Gastroenteritis	5 (35.7)	2 (16.7)	7 (26.9)
Hepatomegaly	6 (42.9)	2 (16.7)	8 (30.8)
Lymphadenopathy	9 (64.3)	5 (41.7)	14 (53.8)
Rhinorrhea	6 (42.9)	11 (91.7)	17 (65.4)
Oral Candidiasis	6 (42.9)	6 (50)	12 (46.2)
Otic Complaint	5 (35.7)	3 (25)	8 (30.8)
Pharyngitis	8 (57.1)	3 (25)	11 (42.3)
Pyrexia	6 (42.9)	7 (58.3)	13 (50)
Rash	8 (57.1)	12 (100)	20 (76.9)
Respiratory Distress	3 (21.4)	1 (8.3)	4 (15.4)
Vomiting	5 (35.7)	2 (16.7)	7 (26.9)

Source: eae.xpt, events.xpt

7.4.2 Laboratory Findings

All subjects had graded toxicities, although very few events were classified as serious, or ≥ Grade 3. Only 8 subjects (31%) had a grade 3 or 4 events. All grade 3 or 4 events

occurred within the first 24 weeks of therapy. The most common events were anemia (8%), neutropenia (8%) and decreased bicarbonate (8%).

Table 17: Grade 3 and 4 Laboratory Events by Preferred Term

Grade 3 or 4 Laboratory Events Preferred Term	Cohort IV N=14 n (%)	Cohort V N=12 n (%)	Total N=26 n (%)
Increased ALT	1 (7.1)	0	1 (3.8)
Anemia	2 (14.2)	0	2 (7.7)
Bicarbonate decreased	1 (7.1)	1 (8.3)	2 (7.7)
Increased bilirubin	1 (7.1)	0	1 (3.8)
Hyperkalemia	0	1 (8.3)	1 (3.8)
Hypocapnia	1 (7.1)	0	1 (3.8)
Hypoglycemia	1 (7.1)	0	1 (3.8)
Increased lipase	1 (7.1)	0	1 (3.8)
Neutropenia	2 (14.2)	0	2 (7.7)

Source: eae.xpt, events.xpt

Grade 3 or 4 adverse events were also very infrequent in cohorts I to III. The small sample size and relative scarcity of grade 3 or 4 events makes comparison difficult. The raltegravir label lists elevation in creatine kinase, neutropenia, anemia, thrombocytopenia, hyperglycemia, hyperbilirubinemia, elevated ALT or AST, elevated alkaline phosphatase, elevated amylase and lipase as possible grade 3 or 4 adverse events. No new safety signal was appreciated in cohorts IV or V.

There were thirty-two hepatic-related laboratory toxicities occurring in fourteen subjects (54%). Most events were Grade 1 or 2, although three episodes of Grade 3 or 4 toxicity occurred in three different subjects.

Table 18: Hepato-biliary Events by Worst Grade Toxicities

	Grade 1	Grade 2	Grade 3	Grade 4
ALT	10	2	1	0
AST	9	4	0	0
Total Bilirubin	0	0	1	0
Alk Phos	0	0	0	0
Lipase	4	0	0	1

Source: PE6815.xpt

Thirty-one total hematological adverse events occurred in 24 subjects (92%). Most events were grade 1 or 2. Two episodes of grade 3 or 4 anemia occurred in two subjects and two episodes of grade 3 neutropenia occurred in two subjects.

Table 19: Hematological Events by Worst Grade Toxicities

	Grade 1	Grade 2	Grade 3	Grade 4
WBC	0	0	0	0
Neutrophils	9	2	2	0
Hemoglobin	13	2	1	1
Platelets	1	0	0	0

Source: PE6810.xpt

7.4.3 Vital Signs

All enrolled subjects had vital signs collected upon entry into the trial and at regular follow-up visits. The applicant reported no clinically significant changes in vital signs. Any clinically significant changes were reported as adverse events, including fever which was reported in 13 (50%) subjects.

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.

7.4.7 Additional Cohort I – III Long Term Safety Data, Week 0 - 144

There were no new deaths in Cohorts I to III since the previous NDA was filed. 31 subjects experienced 73 serious adverse events. The most common clinical serious adverse events not previously reported were depression (4 subjects) and abdominal pain (4 subjects). Four serious adverse events were assessed as possibly related to raltegravir use. Patient 400125 had an episode of grade 2 vaginal bleeding and patient 892125 had an episode of grade 2 drug-induced liver injury. Both episodes resolved without intervention or discontinuation of raltegravir. Patient 380769 developed pancreatitis felt to be possibly related to raltegravir, resulting in permanent discontinuation of raltegravir. Patient 720101 developed abdominal pain felt to be related to raltegravir for which the study drug was temporarily held.

Three subjects permanently discontinued raltegravir as of the February 7th, 2013 cutoff date. Patient 502828 died of pneumonia after (b) (6) days of raltegravir. Her death was determined not to be related to raltegravir therapy. Patient 730032 developed agitation which was not felt to be secondary to raltegravir. The sponsor reports that the patient was admitted to a psychiatric facility that was not capable of administering the medication. Finally, patient 411288 went into septic shock with subsequent renal failure, not felt to be secondary to raltegravir use.

Thirty three subjects experienced 133 clinical grade 3 or 4 adverse events. The most common grade 3 or 4 adverse events not previously reported included abdominal pain (7 subjects), depression (4 subjects), diarrhea (4 subjects), chest pain (3 subjects), convulsion (3 subjects), cough (3 subjects) and headache (3 subjects).

Abdominal pain, headache, psychiatric events such as depression, suicidal ideation and behavior, paranoia, anxiety are included in the current raltegravir label and some of these events were considered by investigators to be related to raltegravir.

Eighteen subjects developed a grade 3 or 4 hematological adverse event. These events included thrombocytopenia (1 patient), anemia (3 subjects) and neutropenia (16 subjects). Twenty one Grade 3 or 4 non-hematological laboratory events occurred in 26 subjects from Cohorts I to III. The most common events were increased ALT (9 subjects), increased AST (6 subjects), increased fasting LDL (3 subjects), increased total bilirubin (4 subjects), increased creatinine (3 subjects). No new safety signal was appreciated, though increased LDL and creatinine are not listed in the current label.

7.5 Other Safety Explorations

No additional safety explorations were conducted. Please refer to the adult NDA for further details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable. Please refer to original NDA review.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable. Please refer to original NDA review.

7.6.3 Pediatrics and Assessment of Effects on Growth

No evidence of decreased growth was observed in Cohorts IV or V while receiving raltegravir. The sponsor has submitted data demonstrating overall upward trends in both weight gain and height during the trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable. Please refer to original NDA review.

7.7 Additional Submissions / Safety Issues

Safety Update Report

Merck submitted a Safety Update Report (SUR) including additional safety data from the time period 8-Feb-2013 to 25-Jul-2013. Only safety data from Cohorts IV and V were included in the reports; Cohorts I – III were discussed in a previous dataset. No additional efficacy data was submitted.

As of 25-Jul-2013, no additional deaths had been reported among the study population. Patient 2020164 died, as discussed in section 7.3.1 above. During the Safety Update Report period, one additional patient discontinued study drug. Patient 2020159 developed pulmonary tuberculosis and was determined to require rifampin by the study investigator. Rifampin is a disallowed medication, and the patient was subsequently permanently discontinued from the trial. No other new serious adverse events (SAE), grade 3 or 4 events were reported for patient 2020159. No other subjects permanently discontinued study drug due to an adverse reaction.

Three additional SAEs were reported in the SUR period. Patient 801538 had an episode of grade 3 hypokalemia that was also reported as an SAE. Patient 8503643 had two episodes of neutropenia reported as SAEs and as grade 3 events. Patient 1270100, who had been discontinued from the study after developing a rash during week one of raltegravir therapy, developed a grade 3 event. In the SUR, he was reported to have a grade 3 episode of increased blood cholesterol. No new SAE, grade 3 or 4 events were attributed to study medication. No new AIDS defining conditions, besides the episode of pulmonary tuberculosis in patient 2020159 discussed above, were reported in the SUR period.

8 Postmarket Experience

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

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

At the time of the completion of this review, labeling negotiations with Merck are ongoing.

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

/s/

BRITTANY GOLDBERG
12/02/2013

YODIT BELEW
12/02/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		Sponsor should submit coding dictionary.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			This NDA submission contains pediatric study conducted in children 4 weeks to 2 years of age.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See above
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

The sponsor should provide the following documentation:

- (1) Written rationale for the applicability of foreign data to a US population
- (2) A coding dictionary consisting of all investigator verbatim terms and the preferred terms to which they were mapped. Please submit as an SAS transport file, or a PDF file with information available both as verbatim to preferred term and preferred term to verbatim.

Brittany Goldberg 8/14/13

 Reviewing Medical Officer Date

Yodit Belew 8/12/13

 Clinical Team Leader Date

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/s/

BRITTANY GOLDBERG
08/14/2013

YODIT BELEW
08/14/2013