CLINICAL AND STATISTICAL REVIEW

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Reviewer Name(s)	Alan M. Shapiro. M.D., Ph.D, Clinical Reviewer Fraser Smith, Ph.D., Biostatistics Reviewer Mary Singer, M.D., Ph.D, Cross-Discipline Team Leader
Review Completion Date	April 8, 2013
Established Name	Efavirenz
Trade Name	Sustiva ®
Therapeutic Class	Non-nucleoside HIV reverse transcriptase inhibitor
Applicant	Bristol-Myers Squibb
Formulation(s)	Capsule, Tablet, Capsule Sprinkles

Dosing Regimen	Once daily efavirenz (dosing varied by clinical trial)
Indication(s)	SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.
Intended Population(s):	Pediatric patients from three months to three years of age.

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the current supplement which extends the indication for Sustiva (efavirenz) use down to three months of age for patients weighing at least 3.5 kg from three years of age for patients weighing at least 10 kg, as currently indicated. This supplement also adds a new method for administering Sustiva (sprinkling and mixing the contents of the approved capsule with various food vehicles including formula for young infants) for both pediatric and adult patients who cannot reliably swallow capsules or tablets. One of the major concerns for this supplement is the ability of patients and/or patient's caregivers to reliably follow the proposed instructions for capsule sprinkle administration. The Applicant must revise the instructions for use of Sustiva capsule sprinkles to facilitate the reliable administration of efavirenz prior to approval of the supplement.

1.2 Risk Benefit Assessment

Sustiva (efavirenz) is an antiretroviral drug with a 15-year successful track record for use. Efavirenz serves as the backbone for many triple antiretroviral drug regimens including once daily Atripla (efavirenz, tenofovir, and emtricitabine). The safety concerns for efavirenz are well known. The major safety concerns for efavirenz include a possible risk of neural tube defects with first trimester pregnancy exposure, rash, seizures, neuropsychiatric adverse events (AEs) and liver toxicity. Also, like many first generation non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz has a low barrier to HIV drug resistance. From the time of the original approval in 1998, the increased frequency of rash, including severe rash in pediatric patients has been described. The data from the current supplement supports this finding. Health care providers and caregivers for pediatric patients need to closely monitor the patient for rash to evaluate whether efavirenz therapy needs to be altered and/or medical management of the rash be undertaken. Neuropsychiatric AEs in pediatric patients were observed in the submitted clinical trials, but did not occur at a high frequency.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended for this supplement.

1.4 Recommendations for Postmarket Requirements and Commitments

The following post-marketing commitments are under discussion with the review team at this time:

1) Perform a label comprehension study to determine whether patients and/or caregivers can understand and follow the instructions for use of Sustiva capsule sprinkles.

(b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

Sustiva (efavirenz) is a non-nucleoside HIV reverse transcriptase inhibitor originally approved in 1998 for treatment of HIV infection. Efavirenz is used as the backbone of many antiretroviral drug regimens; and is recommended as first line therapy in combination with tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve patients with HIV infection.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 shows the antiretroviral agents currently approved for use in pediatric patients.

Table 1: Approved Pediatric Antiretrovirals

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Combivir	lamivudine (LMV) and zidovudine (ZDV),	GlaxoSmithKline	≥ 30 kg
Emtriva	emtricitabine, FTC	Gilead Sciences	0-3 months and above
Epivir	lamivudine, 3TC, LMV	VIIV Healthcare	≥3 months
Hivid (discontinued)	zalcitabine, ddC, dideoxycytidine	Hoffmann-La Roche	≥13 years
Retrovir	zidovudine, ZDV, azidothymidine, AZT	GlaxoSmithKline	≥ 4 weeks and ≥ 4 kg
Trizivir	abacavir (ABC), zidovudine (ZDV), and lamivudine (LMV)	GlaxoSmithKline	Adolescents > 40kg
Truvada	tenofovir disoproxil fumarate and		12 years of age and older and weighing

	emtricitabine		greater than or equal to 35 kg
Videx	didanosine,ddI, dideoxyinosine	Bristol Myers-Squibb	≥ 2 weeks
Videx EC	didanosine delayed release	Bristol Myers-Squibb	≥ 20 kg
Viread	tenofovir disoproxil fumarate (TDF)	Gilead Sciences	≥ 2 years
Zerit	stavudine, d4T	Bristol Myers-Squibb	Birth-13 days and above
Ziagen	abacavir, ABC	GlaxoSmithKline	≥ 3 months
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Intelence	etravirine, ETR	Janssen	≥ 6 years and weighing ≥ 16 kg
Rescriptor	delavirdine, DLV	Pfizer	≥ 16 years
Sustiva	efavirenz, EFV	Bristol Myers-Squibb	≥3 years (≥3 months or 3.5 kg, pending current approval)
Viramune	nevirapine, NVP, BI-RG-587	Boehringer Ingelheim	≥ 15 days
Viramune XR	nevirapine extended release NVP XR	Boehringer Ingelheim	≥ 6 years
Protease Inhibitors (PIs)			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Agenerase (discontinued)	amprenavir, APV	GlaxoSmithKline	≥ 4 years
Aptivus	tipranavir, TPV	Boehringer Ingelheim	≥ 2 years
Invirase	saquinavir mesylate, SQV	Hoffmann-La Roche	≥16 years (Pediatric dose recommendations not made due to

			PR/QT concerns)
Kaletra	lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	≥ 14 days (postmenstrual age of 42 weeks + 14 days)
Lexiva	Fosamprenavir Calcium, FOS	GlaxoSmithKline	≥ 2 years
Norvir	ritonavir, ABT-538, RTV	Abbott Laboratories	>1 month and a post-menstrual age ≥ 44 weeks
Reyataz	Atazanavir, ATV	Bristol-Myers Squibb	> 6 years
Prezista	Darunavir, DRV, TMC-114	Tibotec, Inc.	≥ 3 years and weighing ≥ 10 kg
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	≥2 years
Fusion Inhibitors			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Fuzeon	enfuvirtide, ENF, T-20	Hoffmann-La Roche & Trimeris	≥ 6 years
CCR5 Co-receptor Antagonist –HIV entry inhibitor			
Brand Name	**Generic Name(s)**	**Manufacturer Name**	**Pediatric Use Labeling**
Selzentry	maraviroc, MVC	Pfizer	≥ 16 years
HIV Integrase Inhibitor			
Brand Name	**Generic Name**	**Manufacturer Name**	**Pediatric Use Labeling**
Isentress	raltegravir, RAL	Merck and Co.	≥ 2 years and weighing ≥ 10 kg
Multi-class Combination Products			
Atripla	Efavirenz (EFV), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)	Bristol-Myers Squibb and Gilead Sciences	≥ 12 years and weighing ≥ 40 kg

2.3 Availability of Proposed Active Ingredient in the United States

Currently, there is no shortage of efavirenz in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Efavirenz is part of the non-nucleoside reverse transcriptase (NNRTI) family which currently also includes nevirapine, etravirine, and rilpivirine. Delaviridine is less frequently used because of dosing frequency, number of pills, and less than optimal antiviral activity. Rash, including severe rash, has been reported with all NNRTIs; but with nevirapine, a concomitant systemic hypersensitivity syndrome may develop in some patients. Hypersensitivity is also a concern with etravirine. Serious adverse reactions for nevirapine, including symptomatic hepatitis (including fatal hepatic necrosis) have been described. Liver-related adverse events associated with efavirenz have been mostly increased transaminases, although hepatic failure has also been reported. Patients taking efavirenz and rilpivirine can also have neuropsychiatric adverse events; and peripheral neuropathy has been described in a few patients receiving etravirine.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of an efavirenz oral liquid formulation for pediatric use was particularly challenging because of the potential for oral mucosal irritation, resulting in a burning sensation in the throat/mouth following oral administration. Development efforts identified a solution formulation in a medium chain triglyceride as the only approach for a liquid formulation that showed acceptable palatability. However, pharmacokinetic parameters resulting from the administration of this formulation in infants and children showed increased variability, making identification of an appropriate exposure-based dose in pediatric subjects challenging. The data for the trial, PACTG 382 Cohort 2, which evaluated an investigational 20 mg/mL, sugar-containing, oral liquid formulation of efavirenz for use in pediatric patients 3 months to 8 years of age (b) (4) given the problems with the oral solution (e.g. microbial contamination and poor bioavailability). Efavirenz exposures were suboptimal with regard to AUC; and the volume of oral solution required to achieve target EFV AUC (i.e. > 20 mL) was excessive for young subjects, particularly for those < 3 years of age. Therefore, the Applicant concluded that the use of the oral solution formulation was not preferred for administration in the pediatric population, especially for those < 3 years of age. Instead, mixing of the capsule content with food additives was identified as the most appropriate approach for the administration of EFV in infants and children. The Applicant has provided dosing information in the proposed product labeling in this supplement.

List of Pediatric-Related Regulatory Dates:

09/17/1998 Sustiva original application for 50mg, 100mg, and 200mg capsules for patient 3 years and older was approved based on accelerated approval regulations. Pediatric Written Request (PWR) was issued for a 48 week study open-label, AUC controlled, multicenter study to determine the pharmacokinetics, safety, and antiviral activity of efavirenz in combination with nelfinavir in HIV-1 infected children between the ages of 3 months and 16 years. Dosage form: liquid formulation and 50mg, 75 mg, 100mg, 150mg, and 200 mg capsules. Submission of studies to fulfill PWR must be received by August 1, 1999.

09/17/1999 Extension of receipt due date for studies to fulfill PWR to September 30, 2001

02/09/2000 Applicant fulfilled requirements of accelerated approval. Phase 4 commitment was issued: "Continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data. Additionally, we refer to our Pediatric Written Request letter."

(b) (4)

08/08/2001 Extension of receipt due date for studies to fulfill PWR to June 30, 2003

02/01/2002 Approval of NDA 21-360 provided for the use of Sustiva® (efavirenz) 300 mg and 600 mg tablets.

07/02/2003 Extension of deadline for PWR to June 30, 2003

08/13/2004 NDA 20-972, S-022 and NDA 21-360, S-006 provided for the inclusion of safety and efficacy data through 168 weeks of therapy. PREA post-marketing commitment: Continue with the development of a pediatric program, with emphasis on developing a liquid formulation along with obtaining safety, tolerability, pharmacokinetic and antiviral activity data. Additionally, we refer to our Pediatric Written Request letter.

02/28/2005 PWR amendment to:

- extend the timeframe for submitting report of the study(ies)
- modify the section 'Type of study(ies)' and eliminate the section 'Study design' to allow study designs using antiretrovirals other than nelfinavir
- make it consistent with current Written Requests in format and language (for example, delineating the expected study population)

01/31/2008 Extension of deadline for PWR to January 31, 2010

04/24/2009 Applicant provides update on PK results from Study AI266922 to support capsule sprinkles as part of dosing recommendations for pediatric subjects > 3 months of age.

06/25/2009 DAVP provided feedback supporting the capsule sprinkle approach and provided additional advice.

06/30/2009 DAVP provided product quality comments regarding proposed pediatric NDA supplement.

12/23/2009 Extension of receipt due date for studies to fulfill PWR to December 31, 2011.

05/02/2011 Applicant sent content and format questions to DAVP regarding proposed pediatric supplement to extend age range of efavirenz use down to three months of age.

05/31/2011 DAVP sent responses to Applicant's questions. In the response, DAVP emphasized the importance of obtaining 48 week data for Group 1 of Study AI266922 and willingness to amend the PWR to allow Applicant to acquire additional data.

07/18/2011 Extension of receipt due date for studies to fulfill PWR to December 31, 2012

08/24/2011-
07/17/2012 Multiple communications between Applicant and DAVP to clarify content and format issues for proposed NDA supplement.

07/05/2012 DAVP requested a 90 day safety update (rather than 120 days) because the planned NDA supplement would be a priority review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

As mentioned above, the Division had extensive discussions with the Applicant about the content and design of this supplement. Given the complexity of combining three different

pediatric clinical trials, the Applicant prepared a reasonable supplement that allowed for effective review.

DSI inspections of clinical and analytical sites are currently in progress as part of the quality assurance for this application and any issues identified with these sites will be appended to this review.

3.2 Compliance with Good Clinical Practices

Pending results of the DSI inspections, there are no concerns in this supplement about deviations from Good Clinical Practice (GCP). All three studies were conducted under GCP and there is a statement in each study report to document the Applicant's compliance.

3.3 Financial Disclosures

The Applicant submitted tables of investigator disclosures and provided evidence of multiple attempts to obtain the required information from investigators who declined to complete and submit the disclosure forms. The Applicant also provided a statement from the Pediatric AIDS Clinical Trial Group (PACTG) that many of the investigators were compliant with PACTG's financial disclosure requirements. Of the investigators who supplied financial interest statements, approximately 10 investigators had disclosable information. None of the investigators appeared to have conflict of interests which could contribute to bias or affect integrity of the trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This supplement included data to support efavirenz administration by the capsule sprinkle method. Chemistry, Manufacturing, and Controls (CMC) reviewed the stability testing of drug in food substance and the palatability evaluation of various capsule sprinkle-food including infant formula mixtures in adults. Please see Dr. Stephen Miller's CMC review for full details.

4.2 Clinical Microbiology

Resistance: No samples from Study PACTG 382 were made available to Applicant by the PACTG. Genotypic and phenotypic data were collected for subjects in Studies AI266922 and PACTG 1021. The genotypic resistance profiles at baseline were summarized for in the supplement for treated subjects. Newly emergent genotypic resistance profiles were summarized for treated subjects who met the criteria for resistance testing with HIV RNA ≥ 500 c/mL and had evaluable samples. Please see review by Virology reviewer Lalji Mishra for additional information.

4.3 Preclinical Pharmacology/Toxicology

There was no new pharmacology-toxicology data submitted with this supplement.

4.4 Clinical Pharmacology

Clinical Pharmacology reviewed the data in the supplement and concluded that the systemic exposures of efavirenz after administration of efavirenz as an intact capsule or as capsule contents mixed with different food vehicles were bioequivalent. The data submitted also supported the following pediatric dosing (see Table 2):

Table 2: **Proposed Dosing of SUSTIVA in Pediatrics**

Pediatric Patients at Least 3 Months and at Least 3.5 kg			
weight	**dose**	**weight**	**dose**
3.5 kg to less than 5 kg	*100 mg*	20 kg to less than 25 kg	300 mg
5 kg to less than 7.5 kg	*150 mg*	25 kg to less than 32.5 kg	350 mg
*7.5 kg to less than 15 kg**	200 mg	32.5 kg to less than 40 kg	400 mg
15 kg to less than 20 kg	250 mg	at least 40 kg	600 mg

Note: New dosing recommendations are highlighted in *italics*.
*Dosing recommendations for the 10-15 kg are part of the currently approved prescribing information for Sustiva; new dosing recommendations only apply to the 7.5-10 kg dose group.

See review by Clinical Pharmacology Reviewers Vikram Arya, Ph.D. and Jeffrey Florian, Ph.D. for additional information.

4.4.1 Mechanism of Action

Sustiva (efavirenz) is a non-nucleoside HIV reverse transcriptase inhibitor that binds the HIV reverse transciptase at a non-catalytic site.

4.42 Sprinkle Dosage Form Issues Including Palatability

Study AI266059 was conducted to analyze the bioavailability of efavirenz capsule contents mixed with food vehicles (applesauce, grape jelly, or yogurt) or infant formula relative to the intact capsule formulation. An open label randomized, three-period, three-treatment cross over study design in two treatment groups in twenty four healthy adult subjects (12 subjects/treatment group). On the morning of Days 1, 21, and 41, subjects either received a single oral 600 mg dose (3x200 mg) of efavirenz (EFV) in a 200 mg intact capsule formulation under fasted conditions (Treatment A) or a single 600 mg dose

(3x200 mg) of EFV capsule contents mixed with three possible food vehicles (applesauce, grape jelly, or yogurt) or baby formula (Treatments B-E). On Days 21 and 41, subjects were crossed over to the next treatment as specified by their assigned treatment sequence:

• Treatment A: 600 mg (3x200 mg) EFV intact capsule (fasted).
• Treatment B: 600 mg (3x200 mg) EFV capsule contents mixed with 2 teaspoons of Mott's® Natural Applesauce.
• Treatment C: 600 mg (3x200 mg) EFV mixed with 2 teaspoons of Smucker's ® Concord Grape Jelly.
• Treatment D: 600 mg (3x200 mg) EFV mixed with 2 teaspoons of Stonyfield Farm® Organic Whole Milk Plain Yogurt.
• Treatment E: 600 mg (3x200 mg) EFV mixed with 2 teaspoons of Enfamil® with Iron Baby Formula.

CONCLUSIONS:
• Although not specifically powered, the AUC of efavirenz capsule contents mixed and administered with these food vehicles (applesauce, grape jelly, and yogurt) or baby formula, met bioequivalence criteria for the AUC of the intact capsule formulation administered under fasted conditions.
• Efavirenz can be administered with applesauce, grape jelly, yogurt, or baby formula.
• Grape jelly was the most palatable food vehicle used to administer efavirenz capsule contents.
• Single oral doses (3 x 200 mg) of efavirenz in a 200 mg intact capsule formulation under fasted conditions or of 600 mg capsule contents mixed with three possible food vehicles (applesauce, grape jelly, or yogurt) or baby formula were generally safe and well tolerated when administered to healthy adult subjects.

Reviewer Comments: Although adults found the efavirenz capsule sprinkle-infant formula mixture to be the least palatable, a number of infants in Study AI266922 were able to tolerate the mixture for months. This finding demonstrates that adult and young children have different perceptions of taste and that results in adults are not always predictive of younger children

4.4.3 Pharmacokinetics
The pharmacokinetic data supported the capsule sprinkle administration in pediatric and adult patients who could not take the intact capsule form.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were three major pediatric trials of efavirenz that evaluated the pharmacokinetics (PK), safety, and antiviral activity of the intact capsule, various oral solution formulations,

and the capsule sprinkle. Although the three studies overlapped each other in time, they represent sequential steps in the development of an age-appropriate pediatric formulation. The three pediatric trials included:

Study PACTG 382, a completed Phase 1/2, open-label, 48-week study that was extended to 208 weeks to evaluate pharmacokinetics and safety of efavirenz in combination with nelfinavir and nucleoside reverse transcriptase inhibitors (NRTIs) in antiretroviral (ARV)-naive or -experienced HIV-infected children 3 months to 16 years of age.

Total treated subjects: 102
USA Mainland: 98 subjects
Puerto Rico: 4 subjects

Cohort I: 57 subjects (3-16 years)
Distribution: (2 to <6 yrs) 3.7-5.88 yrs [13-21kg]: 13 subjects (54% male, 46% female)
(6 to <12 yrs) 6.021-11.72 yrs [18-44kg]: 37 subjects (32% male, 68% female)
(12 to <17 yrs) 12.6-16.8 yrs [32-96kg]: 7 subjects (29% male, 71% female)

Cohort II-Strata 1: 26 subjects (3 months - 2 years)
Distribution: (3 – 6 months){one subject 1.9 months} [4.8-7kg]: 11 subjects (55% male, 45% female)
(6 months - < 1 year) [5.7 -11 kg]: 8 subjects (13% male, 87% female)
(1 yr – 2 year) {13 – 24 months},[8.1-14kg]: 7 subjects (43% male, 57% female)

Cohort II-Strata 2: 19 subjects (>2 years - 8 years)
(3 yrs to <10 yrs) [13-25kg]:19 subjects (53% male, 47% female)

Study PACTG 1021, a completed Phase 1/2, open-label, 192-week dose finding study to evaluate EFV in combination with emtricitabine (FTC) and didanosine (ddI) in ARV-naïve (or very limited ARV-exposed) HIV-infected children 90 days to 21 years of age.

Total treated subjects: 43
USA Mainland: 41 subjects
Puerto Rico: 2 subjects

Group 1: 6 subjects (90 days - < 3 years)
Group 2: 21 subjects (3 years to < 13 years)
Group 3: 16 subjects (13 - < 22 year)

Study AI266922, an ongoing, Phase 2, open-label, 48-week dose-finding study evaluating the pharmacokinetics (PK) and safety of EFV as an oral solution formulation and as a capsule formulation given as a sprinkle preparation in combination with ddI and FTC, in ARV-naive or -experienced HIV-infected children 3 months to 6 years of age.

Total treated subjects: 37
Argentina: 4 subjects
Columbia: 1 subject
Mexico: 19 subjects
Panama 4 subjects
South Africa 7 subjects
Thailand 2 subjects

Group 1: 15 subjects (≥3 months - < 6 months)
Group 2: 10 subjects (≥6 months - < 2 years)
Group 3: 4 subjects (≥2 years - < 3 years)
Group 4: 8 subjects (≥3 years - ≤6 years)

Data from the following open access trials were analyzed to support the supplement.

LEAP/NPP Studies (AI266802/AI266803/AI266913/AI266914/AI266916) Open Access. The LEAP/NPP Studies are part of an Ongoing Phase 3b open-label, multicenter, expanded access and named patient program to provide the EFV oral solution to HIV-infected subjects as part of their ARV regimens. Safety, tolerability, and taste were assessed.

Total treated Subjects: 129
3 subjects (2 to < 3 years)
116 subjects (3 to ≥ 12 years)
10 subjects (>12 to < 18 years)

5.2 Review Strategy

This review utilized a combination dataset compiled by the Applicant to merge the study safety results for three efavirenz studies that either used regular capsules, various versions of oral solution, and capsule sprinkles. It is understood that the comparisons of safety between the three studies is imperfect but the Applicant's efforts to harmonize the data has been more than adequate to allow comparisons between the studies. In addition to examining the combined datasets, datasets from the individual studies were also examined. Comparisons were done across age groups and formulations.

5.3 Discussion of Individual Studies/Clinical Trials

PACTG 382

The original pediatric study which initially used the capsule formulation in subjects 3 years to 16 years of age is reflected in the 1998 label. Subsequently, an oral solution was evaluated as part of the study.

PACTG 1021:
This study continued the development of an oral solution and on exploratory basis explored the use of capsule sprinkle.

AI266922:
This study directly compared oral solution to capsule sprinkles. Based on the results of this study, the Applicant selected the capsule sprinkles as an acceptable alternative to the various failed attempts to create an oral solution.

LEAP:
Liquid Expanded Access Program (LEAP) was used to make liquid efavirenz formulation available to pediatric patients who were failing their antiretroviral regimen. Given bioavailability concerns, the doses of the oral solution were larger than the regular capsule formulation. This program involved the collection of data in non-controlled fashion. The frequency of AEs, serious adverse events (SAEs), and discontinuations of study drug due to AEs or laboratory abnormality were recorded.

6 Review of Efficacy

Efficacy Summary

In all three of the major pediatric studies, viral suppression and immunologic response were observed with efavirenz combination therapy across all age groups by Week 48, as measured by HIV RNA, CD4 cell count, and CD4 percent. In the two longer-term studies (PACTG 382 and PACTG 1021), virologic suppression (as measured by HIV RNA) persisted through Week 96 for subjects who remained on study.

6.1 Indication

Efavirenz (Sustiva®) is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 infection.

Methods

Study PACTG 382 was a Phase 1/2 open-label 48-week area under the concentration-time curve (AUC)-controlled study that was extended to 208 weeks to determine the PK, safety, tolerability, and antiviral activity of efavirenz (EFV), in combination with nelfinavir and NRTIs, in ARV-naive or -experienced HIV-infected children 3 months to 16 years of age divided into 2 cohorts.

Study PACTG 1021 was a Phase 1/2 open-label 192-week study designed to evaluate the safety, tolerability, antiviral activity, and PK of EFV, in combination with FTC and ddI, in ARV-naive (or very limited ARV-exposed) HIV-infected children 90 days to 21 years of age.

Study AI266922 is an ongoing, Phase 2 open-label 48-week study to determine the PK, safety, tolerability, and antiviral activity of liquid and capsule sprinkle formulations of EFV, administered in combination with ddI and FTC, in ARV-naive or –experienced HIV-infected children 3 months to 6 years of age. The data cutoff for this study was 08-Feb-2012. This study assessed whether a weight-based dosing algorithm for EFV oral solution and the capsule sprinkle formulation would produce drug exposures (AUC) in the range of 110 to 380 μM•h) comparable to those observed in adults treated with EFV capsules 600 mg daily. Of the 4 age groups in this study, Group 1 (≥ 3 months to < 6 months of age) was the last to complete enrollment (in February 2011), and thus, the last of the Group 1 subjects did not reach the 48-week time point until January 2012.

6.1.1 Formulations Used in Major Studies

Table 3: Description of Efavirenz Formulations Used in Three Major Studies

Formulation	Description	Drug Development Stage Reached	Studies	Reason Leading to Failure
Current Oral Solution	Efavirenz sugar-free oral solution formulation, 30 mg/mL, strawberry-mint flavor	Phase 1	AI266101 (DMP266-101)	The mean Cmax for the oral solution was ~80% that of the capsule dose.
		Phase 2	PACTG 382, PACTG 1021, AI266922, & LEAP studies	Administration of this formulatio in infants and children demonstrated increased variability in the PK parameters that indicated it would be difficu to establish feasible dosing recommendation of the liquid formulation.
Proposed in current supplement	Capsule Sprinkle	Phase 2	PACTG 1021* & AI266922	none

* Only one subject in PACTG 1021 was treated with capsule sprinkle.

6.1.2 Demographics

See Section 7.2.1

6.1.3 Subject Disposition

48 weeks:
In Study PACTG 382, 77% of Cohort I, 62% of Cohort II Stratum 1, and 90% of Cohort II Stratum 2 completed at least 48 weeks of efavirenz therapy. In Study PACTG 1021, 67% of Group 1, 90% of Group 2, and 81% of Group 3 completed at least 48 weeks of efavirenz therapy. In Study AI266922, 60% of Group 1, 90% of Group 2, 75% of Group 3, and 75% of Group 4 completed at least 48 weeks of efavirenz therapy.

96 weeks:
In Study PACTG 382, 60% of Cohort I, 54% of Cohort II Stratum 1, and 73% of Cohort II Stratum 2 completed at least 96 weeks of efavirenz therapy. In Study PACTG 1021, 50% of Group 1, 81% of Group 2, and 69% of Group 3 completed at least 96 weeks of efavirenz therapy. In Study PACTG 1021, 50% of Group 1, 81% of Group 2, and 69% of Group 3 completed at least 48 weeks of efavirenz therapy. There is no 96 week data for Study AI266922.

Reasons for Discontinuation:
In Study PACTG 382, the most common reason for subject discontinuation was reaching a clinical endpoint defined by the protocol, followed by the request of parent or legal guardian, Investigator or Applicant.

In Study PACTG 1021, the most common reason for subject discontinuation was reaching a protocol-defined clinical event, disease progression or laboratory endpoint, followed by subject no longer able to attend clinic.

In Study AI266922, the most common reason for subject discontinuation was lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

For all three pediatric trials, the following efficacy endpoints were evaluated during the treatment period for treated subjects by study at Week 48 (and Week 96 for the 2 PACTG studies):

1) Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL were analyzed by the Applicant using 3 methods including Confirmed Virologic Response (CVR), Virologic Response - Observed Cases (VR-OC), and the Snapshot algorithm. For this review the snapshot algorithm described below was used:

- **Snapshot algorithm** - response rates were assessed using noncompleter equals failure (NC = F) and the last HIV RNA in the predefined analysis week window was used in the analysis.

2) **CD4 Analysis**

- CD4 percent and change from baseline using observed values
- CD4 cell count and change from baseline using 3 different methods including Observed values, Last observed carried forward (LOCF), and Baseline observation carried forward (BOCF). For this review, LOCF approach was used. The LOCF approach was also favored by Applicant because the last on-treatment CD4 value was more clinically relevant to missing values than the baseline value.

Results by Study:

PACTG 382

For PACTG 382, the 48 week snapshot results for Cohort I (capsules) and Cohort II Stratum 2 (oral solution for subjects 2-8 years of age) were similar for HIV RNA < 400 (61-63%) and HIV RNA < 50 copies/mL (51-58%); while Cohort II Stratum 1 (3 months – 2 years of age) had a lower rate of virologic response with an HIV RNA < 400 copies/mL and HIV RNA < 50 copies/mL of 42% and 15%, respectively [see Tables 4 and 5]. Per the Snapshot analysis, most subjects who were classified as virological failures had an HIV viral load > 50 copies/mL. For both cohorts, the median increase from baseline in CD4+ count at 48 weeks of therapy was 111 cells/mm^3 and the median increase in CD4+ percentage was 5%.

Reviewer Comment: The youngest age group 3 months to 2 years of age (Cohort II Stratum 1) had a lower antiviral response to efavirenz oral solution at 48 weeks in comparison to Cohort II Stratum 2 most likely due to the variable pharmacokinetic properties and tolerability of the solution in this young age group. The older age group receiving oral solution (Cohort II Stratum 2) did better with the oral solution and had a comparable antiviral activity to Cohort 1 group which received the intact capsule formulation. Subjects in Cohort II Stratum 2 may have been able to tolerate the oral solution better than the youngest subjects.

Table 4: PACTG 382 Overall Efficacy Summary at Week 48

Snapshot Analysis Results	Cohort I (3 to 16 yrs; EFV capsules) N=57	Cohort II Stratum 1 (3mos to 2yrs; EFV oral solution) N=26	Cohort II Stratum 2 (>2 to 8yrs; EFV oral solution) N=19	Total N=102
HIV RNA < 400 copies/mL	35/57 (61.4%)	11/26 (42.3%)	12/19 (63.2%)	58/102 (56.9%)
HIV RNA < 50 copies/mL	29/57 (50.9%)	4/26 (15.4%)	11/19 (57.9%)	44/102 (43.1%)
CD4 Analysis Results				
CD4, Median Change from Baseline (Q1, Q3) LOCF	n=57 85 (-54, 206)	n=26 92 (-520, 796)	n=19 366 (34, 560)	n=102 111 (-79, 409)
CD4 Percent, Median Change from Baseline (Q1, Q3) Observed	n=43 4 (-1, 8)	n=16 6 (-5,10)	n=17 8 (4,10)	N=76 5 (-3,8)

The following table shows the snapshot analysis including reasons for virologic failure.

Table 5: Snapshot Outcomes at Week 48 (HIV RNA < 50 c/mL) – Treated Subjects in PACTG382

	Number of Subjects (%) Age Group			
	COHORT I N=57	COHORT II N=26	Cohort III N=19	TOTAL N=102
• Virologic success	29 (51%)	4 (15%)	11 (58%)	44 (43%)
• Virologic failure	27 (47%)	18 (69%)	7 (37%)	52 (51%)
❖ HIV RNA>=50 copies/mL	15 (26%)	11 (42%)	6 (32%)	32 (31%)
❖ Discontinued (D/C'd) due to virologic failure	6 (11%)	1 (3.8%)	0	7 (6.9%)
❖ D/C'd due to other reasons and HIV RNA>=50 copies/mL at D/C	6 (11%)	6 (23%)	1 (5.3%)	13 (13%)
• Missing virologic data in Week 48 window	1 (1.8%)	4 (15%)	1 (5.3%)	6 (5.9%)
❖ Discontinued due to AE or death	1 (1.8%)	2 (7.7%)	1 (5.3%)	4 (3.9%)
❖ D/C'd due to other reasons and HIV RNA<50 copies/mL at D/C	0	1 (3.8%)	0	1 (1.0%)
❖ Missing HIV RNA week 48 data but on-treatment	0	1 (3.8%)	0	1 (1.0%)

Note: Eight subjects were excluded from the analyses at Week 96 because they had completed treatment at Week 48 before the protocol was amended to extend the use of study therapy beyond 48 weeks.

At 96 weeks [see Tables 6 and 7], using the snapshot analysis, Cohort II Stratum 2 (oral solution for subjects 2-8 years of age) had a higher virologic response rate than Cohort I (capsules) for both HIV RNA < 400 copies/mL (61% vs. 48%, respectively) and HIV RNA < 50 copies/mL (50% vs. 36%, respectively); while Cohort II Stratum 1 (3 months – 2 years of age) had a lower virologic response with an HIV RNA < 400 copies/mL and HIV RNA < 50 copies/mL of 42% and 15%, respectively. Per the Snapshot analysis, most subjects who were classified as virological failures were on the basis of an HIV viral load > 50 copies/mL. Across all cohorts, the median increase from baseline in CD4+ count at 48 weeks of therapy was 111 cells/mm^3 and the median increase in CD4+ percentage was 5%. At 96 weeks, the median increase from baseline in CD4+ count was 175 cells/mm^3 and the median increase in CD4+ percentage was 7%.

Reviewer Comments: 1) The antiviral activity of efavirenz as a component of a multidrug anti-HIV therapy decreased over time. This has been observed in adults on an efavirenz regimen, and may be reflective of cumulative antiviral resistance slowly developing over time, declining adherence or worsening tolerability over time. At 96 weeks the snapshot analysis confirms that the frequency of virological failure increases over time for most of the subjects except for Cohort II Stratum 1. The subjects in this Cohort – Stratum already have a decreased response at 48 weeks and the subjects who did well at 48 weeks appeared to do well at 96 weeks. This result suggest that in the youngest group receiving oral solution there may be a subset of subjects who can tolerate the oral solution and have an adequate bioavailability and tolerability of the oral solution for effective treatment,

Table 6: PACTG 382 Overall Efficacy Summary at Week 96

Snapshot Analysis Results	Cohort I (3 to 16 yrs; EFV capsules) N=57	Cohort II Stratum 1 (3mos to 2yrs; EFV oral solution) N=26	Cohort II Stratum 2 (>2 to 8yrs; EFV oral solution) N=19	Total N=102
HIV RNA < 400 copies/mL	24/50 (48.0%)	11/26 (42.3%)	11/18 (61.1%)	46/94 (48.9%)
HIV RNA < 50 copies/mL	18/50 (36.0%)	4/26 (15.4%)	9/18 (50.0%)	31/94 (33.0%)
CD4 Analysis Results				
CD4, Median Change from Baseline (Q1, Q3) LOCF	n=57 151 (-37, 311)	n=26 278 (-520, 974)	n=19 264 (-60, 555)	n=102 175 (-102, 469)
CD4 Percent, Median Change from Baseline (Q1, Q3) Observed	n=32 6 (0, 8)	n=14 6 (1,13)	n=14 10 (2,16)	N=58 7 (2,11)

Table 7: Snapshot Outcomes at Week 96 (HIV RNA < 50 copies/mL) – Evaluable Treated Subjects in PACTG382

	Number of Subjects (%) Age Group			
	COHORT I N=50	COHORT II N=26	Cohort III N=18	TOTAL N=94
• Virologic success	18 (36)	4 (15%)	9 (50%)	31 (33%)
• Virologic failure	25 (50%)	18 (69%)	5 (28%)	48 (51%)
❖ HIV RNA>=50 copies/mL	11 (22%)	10 (39%)	4 (22%)	25 (27%)
❖ Discontinued due to virologic failure	7 (14%)	1 (3.8%)	0	8 (8.5%)
❖ D/C'd due to other reasons and HIV RNA>=50 copies/mL at D/C	7 (14%)	7 (27%)	1 (5.6%)	15 (16%)
• Missing virologic data in Week 96 window	7 (14%)	4 (15%)	4 (22%)	15 (16%)
❖ Discontinued due to AE or death	1 (2.0%)	3 (12%)	1 (5.6%)	5 (5.3%)
❖ D/C'd due to other reasons and HIV RNA<50 copies/mL at D/C	1 (2.0%)	1 (3.8%)	2 (11%)	4 (4.3%)
❖ Missing HIV RNA week 96 data but on-treatment	5 (10%)	0	1 (5.6%)	6 (6.4%)

Reviewer Comment: Use of the oral solution in subjects 3 months to 2 years of age in Cohort 2 Stratum I resulted in lower virologic response rates than those observed with oral solution used in older subjects. These results appear to reflect the poor bioavailability and tolerability of the oral solution used in PACTG 382. See Section 6.1.1.

PACTG 1021: The snapshot results for youngest subjects in Group 1(3 months to < 3 years), HIV RNA < 400 copies/mL (50%) and HIV RNA < 50 copies/mL (50%) showed a lower rate of virological response compared to the older subjects in Groups 2 (3 to < 13 years) and Group 3 (13 to <22 years) [see Table 8]. The older subjects in Group 3 had comparable snapshot results to Group 2 for HIV RNA < 400 copies/mL (both 81%) but for HIV RNA < 50 copies/mL , greater antiviral activity was observed in Group 3 than Group 2 (81% versus 67%, respectively). Per the Snapshot analysis, most subjects who were classified as virological failures had an HIV viral load > 50 copies/mL or were discontinued from study drug for virological failure [see Table 9]. The median increase in CD4 count and median CD4 percentage were of smaller magnitude for the youngest subjects Group 1 (165 and 0%, respectively) as compared to the older subjects in Group 2 (238 and 18%, respectively) and Group 3 (216 and 15%, respectively).

Reviewer Comment: The youngest age group 3 months to less than 3 years of age in Group 1 had a lower antiviral response to efavirenz oral solution at 48 weeks as compared to Group 2 for whom 57% of subjects received oral solution and the remaining 43% received capsule. The lower response in Group 1 could be due to the combination of the variable pharmacokinetic properties and tolerability of the oral solution in those subjects and the more reliable pharmacokinetic properties of the intact capsule. The older Group 3 subjects receiving intact capsule had the greatest overall antiviral response again reflecting the more reliable pharmacokinetic properties of the intact capsule.

Table 8: PACTG 1021 Overall Efficacy Summary at Week 48

Snapshot	Group 1 (90 days to <3yrs) N=6 [Oral Solution N=5; Capsule Dispersed N=1]	Group 2 (3 to <13 yrs) N=21 [Oral Solution N=12; Intact Capsule N=9]	Group 3 (13 to < 22 yrs) N=16 [all intact capsule]	Total N=43
HIV RNA < 400 copies/mL	3/6 (50%)	17/21 (81%)	13/16 (81.3%)	33/43 (76.7%)
HIV RNA < 50 copies/mL	3/6 (50%)	14/21 (66.7%)	13/16 (81.3%)	30/43 (69.8%)
CD4, Median Change from Baseline (Q1, Q3) LOCF	n=6 165 (-1341, 780)	n=21 238 (169, 349)	n=16 216 (111, 293)	n=43 221 (132, 349)
CD4 Percent, Median Change from Baseline (Q1, Q3) Observed	n=4 0 (-12, 12)	n=18 13 (10, 17)	n=13 15 (10, 20)	n=35 13 (9, 18)

Table 9: Snapshot Outcomes at Week 48 (HIV RNA < 50 copies/mL) – Treated Subjects in PACTG1021

	Number of Subjects (%) Age Group			
	GROUP 1 N=6	GROUP 2 N=21	GROUP 3 N=16	TOTAL N=43
• Virologic success	3 (50%)	14 (67%)	13 (81%)	30 (70%)
• Virologic failure	3 (50%)	5 (24%)	2 (13%)	10 (23%)
❖ HIV RNA>=50 copies/mL	1 (17%)	3 (14%)	0	4 (9.3%)
❖ Discontinued due to virologic failure	2 (33%)	1 (4.8%)	1 (6.3%)	4 (9.3%)
❖ D/C'd due to other reasons and HIV RNA>=50 copies/mL at D/C	0	1 (4.8%)	1 (6.3%)	2 (4.7%)
• Missing virologic data in Week 48 window	0	2 (9.5%)	1 (6.3%)	3 (7.0%)
❖ Discontinued due to AE or death	0	0	1 (6.3%)	1 (2.3%)
❖ D/C'd due to other reasons and HIV RNA<50 copies/mL at D/C	0	1 (4.8%)	0	1 (2.3%)
❖ Missing HIV RNA week 48 data but on-treatment	0	1 (4.8%)	0	1 (2.3%)

At 96 weeks (see Table 10), the snapshot results for youngest subjects in Group 1(3 months to < 3 years) who were primarily receiving oral solution, with HIV RNA < 400 copies/mL (33%) and HIV RNA < 50 copies/mL (33%) had a lower rate of virological response compared to the older subjects in Groups 2 (3 to < 13 years) and Group 3 (13 to <22 years). The older subjects in Group 3 had comparable snapshot results to Group 2 for HIV RNA < 400 copies/mL (both 67-69%) and HIV RNA < 50 copies/mL results (both 67-69%). Per the Snapshot analysis, most subjects who were classified as virological failures had an HIV viral load > 50 copies/Ml or being discontinued from study drug for virological failure [see Table 11]. The changes in median CD4 count and median CD4 percentage were of smaller magnitude for the youngest subjects Group 1 (-33 and -13%, respectively) as compared to the older subjects in Group 2 (349 and 14%, respectively) and Group 3 (279 and 11%, respectively).

Reviewer Comments: 1) As stated above, the antiviral activity of efavirenz as a component of a multidrug anti-HIV therapy decreased over time. This has been observed in adults and may be reflective of cumulative antiviral resistance slowly developing over time, declining adherence or worsening tolerability. At 96 weeks the snapshot analysis confirms that the frequency of virological failure increases over time for all subject groups except for two-thirds of the subjects in Group 2 continue at 96 weeks to have virological response with HIV RNA <50 copies/mL. The youngest subjects in Group 1 who almost all receive oral solution continued to demonstrate a decreased virological response over time with a HIV RNA <50 copies/mL for 33% of the subjects. This result continues to suggest that in the youngest group did not respond well to the efavirenz oral solution. The

relatively poor antiviral activity results in younger subjects on oral solution continue to reflect the difficulties the Applicant had with their oral solution that had inadequate bioavailability and poor tolerability, and thus lower antiviral activity especially for the youngest subjects. See Section 6.1.1

Table 10: PACTG 1021 Overall Efficacy Summary at Week 96

Snapshot	Group 1 (90 days to <3yrs) N=6 [Oral Solution N=5; Capsule Dispersed N=1]	Group 2 (3 to <13 yrs) N=21 [Oral Solution N=12; Intact Capsule N=9]	Group 3 (13 to < 22 yrs) N=16 [all intact capsule]	Total N=43
HIV RNA < 400 copies/mL	2/6 (33.3%)	14/21 (66.7%)	11/16 (68.8%)	27/43 (62.8%)
HIV RNA < 50 copies/mL	2/6 (33.3%)	14/21 (66.7%)	11/16 (68.8%)	27/43 (62.8%)
CD4, Median Change from Baseline (Q1, Q3) LOCF	n=6 -33 (-1857, 173)	n=21 349 (209, 569)	n=16 279 (188, 352)	n=43 276 (140, 392)
CD4 Percent, Median Change from Baseline (Q1, Q3) Observed	n=3 -13 (-20, 1)	n=15 14 (10, 22)	n=11 17 (14, 23)	n=29 15 (10, 20)

Table 11: Snapshot Outcomes at Week 96 (HIV RNA < 50 copies/mL) – Treated Subjects in PACTG1021

	Number of Subjects (%) Age Group			
	GROUP 1 N=6	GROUP 2 N=21	GROUP 3 N=16	TOTAL N=43
• Virologic success	2 (33%)	14 (67%)	11 (69%)	27 (63%)
• Virologic failure	4 (66.7%)	4 (19%)	2 (13%)	10 (23%)
❖ HIV RNA>=50 copies/mL	1 (17%)	2 (9.5%)	0	3 (7.0%)
❖ Discontinued due to virologic failure	3 (50%)	1 (4.8%)	1 (6.3%)	5 (12%)
❖ D/C'd due to other reasons and HIV RNA>=50 copies/mL at D/C	0	1 (4.8%)	1 (6.3%)	2 (4.7%)
• Missing virologic data in Week 96 window	0	3 (14%)	3 (19%)	6 (14%)
❖ Discontinued due to AE or death	0	0	1 (6.3%)	1 (2.3%)
❖ D/C'd due to other reasons and HIV RNA<50 copies/mL at D/C	0	2 (9.5%)	2 (13%)	4 (9.3%)
❖ Missing HIV RNA week 96 data but on-treatment	0	1 (4.8%)	0	1 (2.3%)

Study AI266922 (Note: Only 48 week results are available for this ongoing study)
The snapshot results [HIV RNA < 400 (60-75%) and HIV RNA <50 (50%)] for subjects six months and older (Groups 2, 3,and 4) were relatively comparable, but subjects 3 to 6 months age did less well (HIV RNA <400 (47%) and HIV RNA <50 (40%) [see Table 12]. Per the Snapshot analysis, most subjects who were classified as virological failures had an HIV viral load > 50 copies/mL [see Table 13]. The median CD4 percent increase varied from 4 to 11% for all four groups**.**

Reviewer Comment: It is difficult to make any definitive conclusion about the relative antiviral activity of the capsule sprinkle versus the oral solution since the number of subjects in each group was relatively small. If an additional subject in Group 1 had achieved an HIV RNA < 50 copies/mL, then one could conclude there was no difference between the various groups of subjects. The results in Table 14 (see analysis by formulation below) support the observation that the antiviral activity of the oral solution and the capsule are comparable.

Table 12: AI266922 Summary of Efficacy Summary at Week 48 (includes subjects who received either oral solution or capsule sprinkles)

Snapshot	Group 1 (≥3 to < 6 mos) N=15 [4 started on oral solution (3 subsequently switched to capsule sprinkles); 11 started on capsule sprinkles]	Group 2 (≥ 6 mos to <2yrs) N=10 [All 10 started on oral solution; 7 subsequently switched to capsule sprinkles]	Group 3 (≥2 to <3yrs) N=4 [3 started on oral solution (2 switched to capsule sprinkle); 1 started on capsule sprinkle]	Group 4 (≥3 to ≤6yrs) N=8 (All 8 started on oral solution and did not change to capsule sprinkle]	Total N=37
HIV RNA < 400 copies/mL	7/15 (47%)	6/10 (60%)	3/4 (75%)	5/8 (63%)	21/37 (57%)
HIV RNA < 50 copies/mL	6/15 (40%)	5/10 (50%)	2/4 (50%)	4/8 (50%)	17/37 (46%)

CD4, Median Change from Baseline (Q1, Q3) LOCF	n=15 44 (-258, 606)	n=10 -61[1] (-1136, 721)	n=4 202 (96, 1077)	n=8 200 (88, 307)	n=37 177 (-28, 606)
CD4 Percent, Median Change from Baseline (Q1, Q3) Observed	n=5 5 (-2, 7)	n=8 4 (-4, 11)	n=2 8 (-1, 17)	n=5 11 (9, 12)	n=20 6 (-1, 13)

[1] Note for Observed Cases, n=8, median=+346

Table 13: Snapshot Outcomes at Week 48 (HIV RNA < 50 copies/mL) – Treated Subjects in AI266922

	Number of Subjects (%) Age Group				
	GROUP 1 N=15	GROUP 2 N=10	GROUP 3 N=4	GROUP 4 N=8	TOTAL N=37
• Virologic success	6 (40%)	5 (50%)	2 (50%)	4 (50%)	17 (46%)
• Virologic failure	6 (40%)	5 (50%)	1 (25%)	4 (50%)	16 (43%)
❖ HIV RNA >= 50 copies/mL	3 (20%)	4 (40%)	1 (25%)	2 (25%)	10 (27%)
❖ Discontinued due to virologic failure	2 (13%)	0	0	0	2 (5.4%)
❖ Discontinued due to other reasons & HIV RNA >= 50copies/mL at D/C	1 (6.7%)	1 (10%)	0	2 (25%)	4 (11%)
• No virologic data in Week 48 window	3 (20%)	0	1 (25%)	0	4 (11%)
❖ Discontinued due to AE or death	3 (20%)	0	1 (25%)	0	4 (11%)
❖ Discontinued due to other reasons & HIV RNA < 50copies/mL at D/C	0	0	0	0	0
❖ Missing HIV RNA week 48 data but on-treatment	0	0	0	0	0

Reviewer Comment: The relatively poor antiviral activity results in younger subjects on oral solution continue to reflect the difficulties the Applicant had with their oral solution that had inadequate bioavailability and thus lower antiviral activity especially for the youngest subjects. See Section 6.1.1

Analysis by Formulation for Study AI266922 :
Overall, when comparing the antiviral activity (HIV RNA <50) for all age groups, the oral solution and capsule sprinkles showed similar antiviral activity (43% and 48%, respectively, as shown in Table 14). No comparisons were made for the formulation age subgroups because the number of subjects in each formulation age subgroup was small, making comparisons difficult.

Table 14: Study AI266922 Antiviral Activity All Ages

	HIV RNA < 50 (n/N)
Oral Solution	6/14 (43%)
Capsule Sprinkle	11/23 (48%)

Reviewer Comments: Overall, the capsule sprinkle formulation performed as well as the oral solution in AI266922. For this reason, and favorable pharmacokinetics, the Applicant has chosen the capsule sprinkles as the pediatric age-appropriate formulation for use in pediatric patients unable to swallow an intact capsule.

Analysis by Antiretroviral Experience for All Studies:

Antiretroviral experience was examined as a factor in the subjects' response to varying efavirenz formulations in all three studies. The numbers involved were too small to make any reasonable or definitive conclusions.

Overall Conclusions regarding Efficacy (Antiviral Activity) in Sustiva Pediatric Trials (see Tables 15 [HIV RNA > 50 copies/mL] and 16 [HIV RNA > 400 copies/mL]):

1. In PACTG 382, efficacy in subjects at least 3 year old was greater than in those younger than 3 years old. This may be due to inadequate exposures to efavirenz administered by oral solution in the younger subjects (also see Tables 5 and 6].

2. In PACTG 1021, efficacy in subjects at least 3 years old was greater than in those younger than 3 years old, although efficacy in youngest group was improved in comparison to PACTG 382. Conclusions regarding efficacy are limited by small numbers in youngest group, and in many cases, those subjects received primarily oral solution (1 of 6 subjects received capsule sprinkles).

3. In the BMS Trial AI266922, efficacy was similar in younger and older subjects (< 3 year vs > 3 yrs). This was only trial were capsule sprinkles were used alone for some subjects, (i.e. without dosing with oral solution first).

4. Overall, the efficacy data are limited by the small numbers of subjects enrolled under 3 years old; there could be some confounding by including both ART-naïve and ART-experienced subjects even if no baseline NNRTI resistance was detected; and for subjects in PACTG 382, the ART regimen used (nelfinavir plus efavirenz plus an NRTI) would not be considered optimal today.

5. Despite the limitations of these data, antiviral activity of efavirenz dosed as capsule sprinkles in pediatric subjects 3 months to 3 years old was demonstrated, particularly in AI26669. Efficacy in adults can be extrapolated to pediatric patients if the appropriate pharmacokinetic parameters can be matched, a pediatric dosing regimen can be identified, and antiviral activity can be demonstrated in pediatric patients.

Table 15: Analysis of Antiretroviral Activity By Age for HIV RNA < 50 copies/mL
HIV RNA < 50 copies/mL at 48 weeks

	48 weeks	**96 weeks**	**48 weeks**	**96 weeks**
Trial	**3 months-< 3 years n/N (%)**	**3 months-< 3 years n/N (%)**	**> 3 years n/N (%)**	**> 3 years n/N (%)**
382 (TN and TE) EFV+Nelfinavir + NRTI				
Formulations	Oral solution	Oral solution	Capsules/Oral solution	Capsules/Oral solution
<50 copies/mL	4/26 (15%)	4/26 (15%)	40/76 (53%)	27/68 (40%)
1021 (TN) EFV+FTC+DDI				
Formulations	Oral solution(almost all) /capsule sprinkle (N=1)	Oral solution(almost all) /capsule sprinkle (N=1)	Capsules/Oral solution	Capsules/Oral solution
< 50 copies/mL	3/6 (50%)	2/6 (33%)	27/37 (73%)	25/37 (68%)
AI26922 (TN and TE) EFV+FTC+DDI				
Formulations	Oral solution or capsule sprinkles	Not available	Oral solution	Not available
< 50 copies/mL	13/29 (45%)	Not available	4/8 (50%)	Not available

Table 16: Analysis of Antiretroviral Activity By Age for HIV RNA < 400 copies/mL

Analysis: < 400 copies/mL at 48 and 96 weeks (< 3 years vs. > 3 years of age)

	48 weeks	96 weeks	48 weeks	96 weeks
Trial	3 months-< 3 years n/N (%)	3 months-< 3 years n/N (%)	> 3 years n/N (%)	> 3 years n/N (%)
382 (TN and TE) EFV+Nelfinavir + NRTI				
Formulations	Oral solution	Oral solution	Capsules/Oral solution	Capsules/Oral solution
<400 copies/mL	11/26 (42%)	11/26 (42%)	47/76 (62%)	35/68 (51%)
1021 (TN) EFV+FTC+DDI				
Formulations	Oral solution(almost all) /capsule sprinkle (N=1)	Oral solution(almost all) /capsule sprinkle (N=1)	Capsules/Oral solution	Capsules/Oral solution
< 400 copies/mL	3/6 (50%)	2/6 (33%)	30/37 (81%)	25/37 (68%)
AI26922 (TN and TE) EFV+FTC+DDI				
Formulations	Oral solution or capsule sprinkles	Not available	Oral solution	Not available
< 400 copies/mL	16/29 (55%)	Not available	5/8 (63%)	Not available

7 Review of Safety

Safety Summary

The frequency of efavirenz AEs was similar to that observed in adults except that pediatric patients were observed to have higher frequency of rash AEs, including higher frequency of Grade 3-4 events (e.g. erythema multiforme). However, no adverse events of Stevens-Johnson syndrome or toxic epidermolysis were described in the pediatric trials. The frequency of neuropsychiatric AEs and liver test (e.g. AST, ALT) abnormalities were not significantly higher than in adults.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Efavirenz was studied in pediatric patients in three controlled clinical studies which utilized either capsule, oral solution, or capsule sprinkles added to a food substance including apple sauce, grape jelly and yogurt or infant formula. The three major studies and the Liquid Expanded Access Program (LEAP)/ Named Patient Program (NPP) are summarized in Section 5.1.

7.1.2 Categorization of Adverse Events (AEs)

The 1994 Division AIDS (DAIDS) AE grading table was used in Studies PACTG 1021 and PACTG 382; and the 2004 DAIDS AE grading table was used in Study AI266922. Therefore, the integrated AE tables represent grading based on 2 different grading criteria. Based on discussions with the Applicant, DAVP (May 2012) was assured that grading criteria for specific safety events of special interest for EFV (neurologic events, rash, and liver toxicity) showed reasonable correspondence. For the integrated AE presentations in this document, the investigators' AE reported terms for Studies PACTG 1021 and PACTG 382 were re-coded using MedDRA version 14.1 (also used for the AI266922 Week 48 CSR) so as to maintain consistency across the 3 studies. Standard AE presentation format grouped by system organ class(SOC) was provided. A total of 69 unique verbatim terms (64 referenced in communications with the DAVP, dated 19-Apr-2012 and 26-Apr-2012, plus an additional 5 identified subsequently) did not meet the Applicant's criteria for standard coding algorithms and could not be coded without further queries. Because queries were not possible for the completed PACTG studies, these events were remapped to MedDRA version 14.1 by migrating the version 11.1 preferred terms (PTs) that had been previously assigned by the PACTG through standard MedDRA mapping across versions.

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

The three controlled clinical trials which examined various formulations of efavirenz (capsules, oral solution, and capsule sprinkles) in different pediatric age groups had similar adverse events to those described in adult subjects treated with efavirenz. However, the frequency of these adverse events varied between the three clinical trials. As stated above, there were differences in AE grading (DAIDS scale) and AE coding (MedDRA). The Applicant attempted to harmonize the adverse events for all three studies into combined datasets called AECOMB which was used to analyze all three studies together. However, the investigators in different studies did not grade infection-related AEs in the same way. For example, in AI266922, the investigators graded infection-related AEs while the investigators in PACTG382 and PACTG1021 did not.

7.2 Adequacy of Safety Assessments

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

The two PACTG studies represent pediatric HIV treatment experience from a somewhat earlier period than the ongoing Study AI266922:
− PACTG 382 was conducted from November 1997 through January 2007.
− PACTG 1021 was conducted from September 2001 to January 2009.
− Ongoing AI266922 data presented in this submission cover the period from February 2007 through February 2012.

Study enrollment criteria and definitions of "naive" varied, and all studies permitted limited prior use of ARVs in the naive population; PACTG 382 had a more experienced population with 87% of all subjects had some prior ARV experience, although the prior treatment agents were almost exclusively limited to NRTIs: but only 4% had any prior experience with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs). In Study PACTG 1021, enrolled subjects were to be naive, considered as having ≤ 56 days of perinatal prophylaxis or < 7 days of cumulative ARV treatment. Prior treatment experience was limited, with only 4 of 43 total subjects (9%) having any documented experience with prior use concentrated in the < 3-year-old group (3 out of 4subjects).

Study AI266922 enrolled both ARV-naive subjects (defined as < 7 days of prior therapy and including infants who had perinatal exposure to ARVs) as well as ARV-experienced children, but all subjects had baseline screening to document sensitivity to the study regimen. Overall, 13/37 (35%) treated subjects had any documented prior ARV exposure; and again, prior exposure was concentrated in the youngest age group, with 10 of 15 subjects in Group 1 (≥ 3 to < 6 months old) having previous ARV exposure.

Exposure by Study (see Section 7.1.1 for cohort and age group definitions)

Study PACTG 382
The median time on study therapy for subjects in all cohorts was 118 weeks (range: 0.1 to 226 weeks). Subjects in Cohort II-Stratum 2 had a longer median time on study therapy (139 weeks) compared with the subjects in Cohort I and in Cohort II-Stratum 1 (104 and 109 weeks, respectively).

Study PACTG 1021
The median time on EFV for all subjects was 181 weeks. Median time on study therapy was longer in the two older age groups (205 and 164 weeks in Groups 2 and 3, respectively) compared with the youngest age group (95 weeks in Group 1).

Study AI266922
The data cutoff for this study was 08-Feb-2012 for the Week 48 analysis. Of the four age

groups in this study, Group 1 was the last to complete enrollment (in February 2011), and thus, the last of the Group 1 subjects did not reach the 48-week time point until January 2012.

Overall, the median time on study therapy at data cutoff was 60 weeks (range: 0.1 to 225 weeks) Median time on study therapy was longer in the older age groups that had completed enrollment earlier (147, 101, and 117 weeks in Groups 2, 3, and 4, respectively) compared with the youngest age group (53 weeks in Group 1).
Overall, 24 subjects (14, 7, and 3 subjects in Groups 1, 2, and 3, respectively) received the EFV capsule sprinkle. None of the four subjects in Group 4 took the capsule sprinkle. Among the 24 subjects who received the capsule sprinkle, the overall median time on capsule sprinkle was 60 weeks (range: 1 to194 weeks). Median time on capsule sprinkle at data cutoff was longer in the older age groups (158 and 142 weeks in Groups 2 and 3, respectively) compared with the youngest age group (51 weeks in Group 1).

Prior to Amendment 3 of the protocol, all subjects initiated treatment with oral solution. Among the 24 subjects who received the capsule sprinkle, 12 subjects had also initially received EFV oral solution (3, 7, and 2 in Groups 1, 2, and 3, respectively). Median time on EFV oral solution was similar in all 3 groups (12, 10, and 11 weeks in Groups 1, 2, and 3, respectively).

Demographics
The targeted age distribution for each study differed, as did the geographic distribution of subjects. Study AI266922 had the youngest population (mean and median ages of 1.7 and 0.7 years, respectively) and Study PACTG 1021 had the oldest (mean and median ages of 10.1 and 9.6 years, respectively). Overall, gender was generally balanced across these populations, with the overall integrated population (n=182) being 52% female. Overall, 51 percent were Black or African American and 28% were Hispanic or Latino, with race and ethnicity distributions generally consistent for subjects younger and older than three years of age. With respect to disease characteristics at baseline, since HIV ribonucleic acid (RNA) levels and CD4 counts vary with age, global numeric comparisons for these variables are less informative, and are consistent with the expected patterns across age groups. As previously discussed, a higher proportion of subjects in Study PACTG 382 had prior treatment experience (primarily nucleoside analogue) than in either of the other 2 trials.
Overall demographics across the 3 key pediatric studies are summarized in Table 17.

Baseline HIV viral load and CD4 count varied by age. The infants and young children less than three years of age had a higher HIV viral load with 50% of subjects with >500,000 copies/mL and a median CD4 count of approximately 1,500 (see Table 18). The children three years and older tended to have lower HIV viral loads with approximately 50% subjects with <30,000 copies/mL and a lower median CD4 count of approximately 560.

Reviewer Comments: In normal pediatric immunodevelopment in non-HIV infected children, CD4 counts are greater than 1500 in infants and decrease over time to 500-750

by the time a child is 13 years of age. Infants tend to have very high HIV viral loads compared to older children.

Table 17: Demographics of all Three Studies

Characteristic	PACTG 382 (N = 102)	PACTG 1021 (N = 43)	AI266922 (N = 37)
Age (years)			
Mean (SD)	5.950 (4.1325)	10.084 (6.7110)	1.664 (1.6659)
Median	5.676	9.593	0.663
Range	0.159 - 16.813	0.274 - 21.109	0.296 - 6.976
Gender, N (%)			
Male	41 (40.2)	22 (51.2)	24 (64.9)
Female	61 (59.8)	21 (48.8)	13 (35.1)
Race, N (%)			
White	28 (32.2)	10 (26.3)	24 (64.9)
Black or African American	58 (66.7)	27 (71.1)	7 (18.9)
Unknown	14 (13.7)	5 (11.6)	0
Asian	0	0	2 (5.4)
Other	0	0	4 (10.8)
American Indian	0	1 (2.6)	0
American Indian/Alaskan Native	1 (1.1)	0	0
Subject Does Not Want to Report	1 (1.1)	0	0

Table 18: HIV RNA Level, CD4 Cell Count, CD4 Percent at Baseline by Age - Treated Subjects (Studies PACTG 382, PACTG 1021, and AI266922)

	<3 years N=61	≥ 3 years N=121	TOTAL
HIV RNA (log_{10} c/mL)			
Mean (SE)	5.4 (0.10)	4.4 (0.07)	4.7 (0.07)
SD	0.80	0.73	0.87
Median	5.8	4.6	4.8
Q1, Q3	5.0, 5.9	3.8, 4.9	4.1, 5.5
Min, Max	2.1, 6.7	2.6, 5.9	2.1, 6.7
Missing	0	0	0
HIV RNA Category	8 (13)	57 (47)	65 (36)
<30,000 - <100,000	4 (6.6)	39 (32)	43 (24)
100,000 - <500,000	18 (30)	18 (15)	36 (20)
500,000 - ≤750,000	6 (9.8)	4 (3.3)	10 (5.5)
> 750,000	25 (41)	3 (2.5)	28 (15)
CD4 Counts (cells/mm^3)			
Mean (SE)	1640 (140)	660 (45)	980 (63)
SD	1030	490	840
Median	1520.00	560.00	700.00
Q1, Q3	752, 2440	340, 800	390, 1360
Min, Max	27, 4050	3, 2330	3, 4050
Missing	4	1	5

Table 18 adapted from Applicant's Summary of Clinical Safety Table S.3.2

7.2.2 Explorations for Dose Response

In dosing pediatric subjects, the Applicant matched adult exposures primarily by AUC There was no clear correlation in these trials between efavirenz Cmax and adverse events. For pediatric subjects with neuropsychiatric, skin or liver-related adverse events who also pharmacokinetic measurements for the dose at which the AE occurred, the Applicant plotted their efavirenz Cmax in comparison to subjects without adverse events (see Figure 1).

Figure 1: Categories of Adverse Events of Interest Versus Observed Efavirenz Cmax by Formulation in Study AI266922

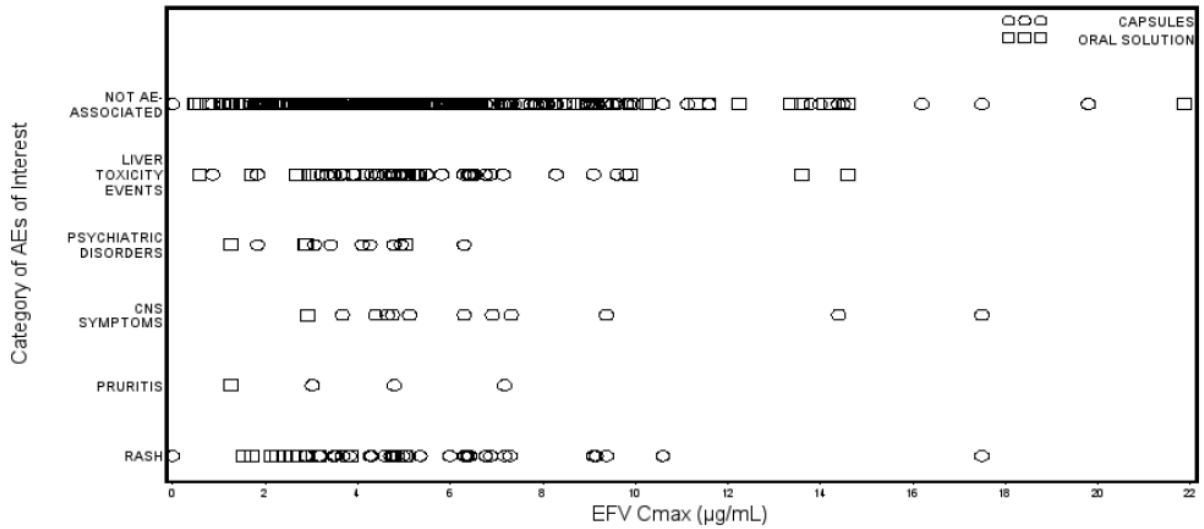

Figure 1 excerpted from Applicant's Summary of Clinical Pharmacology Studies Figure 3.2.3A

Note: Capsule sprinkle and intact capsule are both represented by open circles.
Cmax = maximum concentration and "Not AE-Associated" = adverse event of interest reported at a formulation and dose of EFV that did not have a corresponding pharmacokinetic record for that subject Liver toxicity events (by AE terms)= elevated GGT, elevated ALT, elevated AST. or LFT abnormal or hepatic enzyme increase. Psychiatric disorders (by AE terms) = abnormal dreams, depression, insomnia, major depression, nightmares, and thinking abnormal. CNS symptoms (by AE terms)= ataxia, balance disorder, disturbance in attention, dizziness, lethargy, psychomotor hyperactivity, somnolence, abnormal dreams. Pruritis (by AE terms)=prurigo and pruritis. Rash (by AE terms)=dermatitis, dermatitis allergic, erythema, erythema multiforme, photodermatosis, rash, rash erythematous, rash generalized, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin reaction and urticaria

7.2.4 Routine Clinical Testing

ECGs were not conducted in any of the three key pediatric trials (PACTG382, PACTG1021, and AI266922). Vital signs and physical examinations were conducted at protocol-defined visits in the three trials, and in some cases, growth abnormalities were reported as AEs. In Studies PACTG 382 and PACTG 1021, no formal analyses of vital signs or physical examination results were conducted. In Study AI266922, vital signs were analyzed by age groups.

7.2.5 Metabolic, Clearance, and Interaction Workup

EFV exposure was associated with CYP2B6 SNPs; however, data was not robust enough to make any definitive conclusions about genotype and clearance. It is notable that a majority of subjects that exhibited SNP mutations associated with reduced EFV clearance were heterozygous for the mutation(s). Heterozygosity of the CYP2B6 516G>T

substitution (GT) appears to have less impact on EFV exposures relative to homozygosity for the substitution (TT). Haas et al (2004) [see Appendix 9.1] reported an approximate 1.4-fold increase in EFV AUC in adult subjects that were heterozygous for the CYP2B6 516G>T substitution relative to subjects that were homozygous wild type (GG); while subjects that were homozygous for the mutation (TT) demonstrated an approximate 3-fold increase in EFV AUC relative to homozygous wild-type subjects.

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

7.3 Major Safety Results

The AEs of concern for efavirenz, including skin, neuropsychiatric and liver function abnormalities, will be examined and compared for all three studies.

7.3.1 Deaths

In the three major pediatric trials, there were five deaths in enrolled subjects. However, only two deaths occurred during treatment with efavirenz. The deaths in the two subjects who died while on EFV therapy in AI266922 were related to an infectious process. See Appendix 9.4 for death narratives.

PACTG382
One subject (PACTG382-6704-500082) died of staphylococcal sepsis more than one year after the last dose of study medication.

Study PACTG 1021
No deaths were reported.

Study AI266922
Through the data cutoff for the Week 48 analysis (08-Feb-2012), 4 subjects had died (3 in Group 1 and 1 in Group 3).

Two subjects in Group 1 died before receiving treatment:
- Subject AI266922-4-39, a white female 5 months of age, died of septic shock
- Subject AI266922-19-27, a white female 4 months of age, died of sepsis.

Two subjects died after initiating study treatment:
- Subject AI266922-27-51 in Group 1, a black South African female 3 months of age, died on Day (b) (6) due to a bacterial infection. She had a history of bacterial sepsis and esophageal candidiasis prior to initiation of study therapy, and there was no evidence of immune reconstitution inflammatory syndrome. She died unexpectedly at home. Her parents did not seek medical attention and no treatment was reported.
- Subject AI266922-5-20 in Group 3, a white female 2. years of age died on Day (b) (6) from heart failure due to complications from pneumonia. One week prior to her

death, her viral load (HIV RNA) was < 50 c/mL, her CD4 cell count was 743 cells/mm^3, and her CD4 percent was 23%.

Reviewer Comment: Even with effective multi-drug HIV therapy and mild to moderate immunosuppression, young pediatric HIV patients (< 5 years of age) are still susceptible to serious life threatening infections that can occur in healthy children at a much lower frequency.

7.3.2 Nonfatal Serious Adverse Events

In comparing SAEs across the three major studies, the infection-related SAEs were excluded from the comparison table since they were only coded for study AI66922. The frequency of SAEs were lower in Study PACTG 1021 (14% [6/43]) as compared to Study PACTG 382 (26% [27/102]) and Study AI266922 (22% 8/37]) [see Table 19]. With the exception of blood and lymphatic and skin related SAEs, most SAEs occurred at a frequency of less than 5%. It is also notable that most SAEs were reported in only 1 or 2 subjects in each of the three trials. Exceptions included neutropenia, which was reported in 6 subjects in PACTG 382, and rash or maculopapular rash, reported in 5 and 8 subjects, respectively, in PACTG 382. Because of the relatively small number of subjects in these trials and low frequency of SAEs, comparison of rates across trials is difficult.

Blood and lymphatic SAEs including neutropenia and thrombocytopenia were more common in Study PACTG 382 (9%) than in Study PACTG 1021 (2%) and Study AI266922 (3%). In reviewing the narratives for neutropenia SAEs, the concomitant antiretrovirals include lamivudine, stavudine, didanosine, emtricitabine, and nelfinavir. Of these antiretrovirals, lamivudine, didanosine, and stavudine have been associated with neutropenia.

Skin related SAEs including rash and maculopapular rash were significantly more common in Study PACTG 382 (16% [16/102]) than in Study PACTG 1021 (5% [2/43]) and Study AI266922 (3% [1/37]).

Subject 1021-5051-507029 (Study PACTG 1021) was coded as having a gastrointestinal SAE (diarrhea and dehydration), and also had severe rash that was classified as erythema multiforme.

Narrative for Subject 1021-5051-507029:
The 17.4 year old subject initiated therapy with efavirenz 600 mg, emtricitabine 200 mg and didanosine 400 mg on 25-Mar-2002 (Day 1). On 27-Mar-2002 (Day 3), the subject developed rash (maculo-papular) over her entire body. On 28-Mar-2002 (Day 4), she experienced swelling of the lips consistent with angioedema with a fever of 102.3°F and lymphadenitis. The event of rash was judged by the investigator to be severe and possibly/probably related to the study medication. She was treated with Zyrtec® for the event of rash.

On 28-Mar-2002 (Day 4), the subject developed diarrhea with vomiting, pyrexia and dehydration. The event of diarrhea was judged by the investigator to be life-threatening and the relationship to study drug was considered "unable to judge". On [redacted] (Day [redacted], the subject had a continued rash with fever, diarrhea and vomiting for four days. On [redacted] a skin biopsy was performed and the result revealed erythema multiforme. She was admitted to the hospital for dehydration and diarrhea. The event of pyrexia and dehydration were judged by the investigator to be severe and relationship unable to judge. The event of diarrhea was judged by the investigator to be life-threatening and relationship unable to judge. The subject was treated with Tylenol® for the event of pyrexia. No concomitant medications were reported for treatment of diarrhea and dehydration. Resolution date was not available for the events of diarrhea, pyrexia, and dehydration; however, the event of rash resolved on 16-Apr-2002 (Day 23). The study medication was discontinued due to the event of rash, diarrhea, pyrexia, and dehydration with the last dose received on 26-Mar-2002 (Day 2).

Neurological SAEs were of relatively low frequency: 5% [2/43] in Study PACTG 1021 and 5% [2/37] in Study AI266922. No neurological SAEs were reported in Study PACTG 382. Psychiatric SAEs were of very low frequency, 2% or less in all three studies. The two SAEs of seizures were in a four month old infant with history of prior seizure and a febrile seizure in a 17 month old. The 17 month old had a concomitant fever at time of convulsions and a negative infectious work up including examination of CSF.

There were no liver-related SAEs reported in the three studies.

The infection-related SAEs which occurred at a frequency of 29% [16/37] in Study AI266922 were examined separately in Table 20. Pneumonia (14% [8/37]) and gastroenteritis (5% [3/37]) were the most frequent infection-related SAEs.

Table 19: SAEs Comparison Across Three Studies excluding Infection-Related SAEs

		AI266-922** (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total (N=182)
Full name of the System Organ Class	**Full name of the MedDRA Preferred Term**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		**1 (2.7%)**	**1 (2.3%)**	**9 (8.8%)**	**11 (6.0%)**
	ANAEMIA	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	NEUTROPENIA	1 (2.7%)	1 (2.3%)	6 (5.6%)	8 (4.4%)
	THROMBOCYTOPENIA	0 (0.0%)	0 (0.0%)	2 (2.0%)	2 (1.1%)
GASTROINTESTINAL DISORDERS		**1 (2.7%)**	**2 (4.7%)**	**3 (2.9%)**	**6 (3.3%)**
	ABDOMINAL PAIN	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
	DIARRHOEA	0 (0.0%)	1 (2.3%)	2 (2.0%)	3 (1.6%)
	INTESTINAL PERFORATION	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	PANCREATITIS	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	VOMITING	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		**1 (2.7%)**	**1 (2.3%)**	**0 (0.00%)**	**2 (1.1%)**
	MASS	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		**0 (0.00%)**	**0 (0.00%)**	**1 (1.0%)**	**1 (0.55%)**
	OVERDOSE	0 (0.00%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
METABOLISM AND NUTRITION DISORDERS		0 (0.0%)	**1 (2.3%)**	0 (0.0%)	**1 (0.55%)**
	DEHYDRATION	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
NERVOUS SYSTEM DISORDERS		**2 (5.4%)**	**2 (4.7%)**	0 (0.0%)	**4 (2.2%)**
	DIZZINESS	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
	EPILEPSY	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	FEBRILE CONVULSION	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	HEADACHE	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
PSYCHIATRIC DISORDERS		**0 (0.0%)**	**1 (2.3%)**	**1 (1.0%)**	**2 (1.1%)**
	PSYCHOTIC DISORDER	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	THINKING ABNORMAL	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		**1 (2.7%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (1.1%)**
	ASTHMA	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	BRONCHIAL HYPERREACTIVITY	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		**1 (2.7%)**	**2 (4.7%)**	**16 (15.7%)**	**19 (19%)**
	ECZEMA	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	ERYTHEMA	0 (0.00%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	PRECANCEROUS SKIN LESION	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
	RASH	0 (0.00%)	1 (2.3%)	5 (4.9%)	6 (3.3%)
	RASH MACULO-PAPULAR	0 (0.0%)	0 (0.0%)	8 (7.8 %)	8 (4.4%)
	RASH PAPULAR	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	RASH PRURITIC	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	URTICARIA	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
VASCULAR DISORDERS		**0 (0.0%)**	**0 (0.0%)**	**1 (1.0%)**	**1 (0.55%)**
	RAYNAUD'S PHENOMENON	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
TOTAL NUMBER OF SAE		**8 (22%)**	**6 (14%)**	**27 (26%)**	**41 (23%)**

**Infection related SAEs not included from Study AI66922 since they were not recorded as SAEs in other studies

Table 20: SAEs in Study AI66922

Full name of the System Organ Class	Full name of the MedDRA Preferred Term	Subjects (N=37)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		**1 (1.79%)**
	NEUTROPENIA	1 (1.79%)
GASTROINTESTINAL DISORDERS		**1 (1.79%)**
	INTESTINAL PERFORATION	1 (1.79%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		**1 (1.79%)**
	MASS	1 (1.79%)
INFECTIONS AND INFESTATIONS		**16 (28.57%)**
	APPENDICITIS PERFORATED	1 (1.79%)
	BACTERIAL INFECTION	1 (1.79%)
	BOVINE TUBERCULOSIS	1 (1.79%)
	BRONCHIOLITIS	1 (1.79%)
	GASTROENTERITIS	3 (5.36%)
	HERPES ZOSTER	1 (1.79%)
	IMPETIGO	1 (1.79%)
	LYMPH NODE TUBERCULOSIS	1 (1.79%)
	MASTOIDITIS	1 (1.79%)
	ORAL CANDIDIASIS	1 (1.79%)
	ORAL HERPES	1 (1.79%)
	OTITIS MEDIA	1 (1.79%)
	PNEUMOCYSTIS JIROVECI PNEUMONIA	1 (1.79%)
	PNEUMONIA	8 (14.29%)
	RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS	1 (1.79%)
	VARICELLA	2 (3.57%)
	VIRAL RASH	1 (1.79%)
	VIRAL UPPER RESPIRATORY T	1 (1.79%)
NERVOUS SYSTEM DISORDERS		**2 (3.57%)**
	EPILEPSY	1 (1.79%)
	FEBRILE CONVULSION	1 (1.79%)
THORACIC AND MEDIASTINAL DISORDERS		**2 (3.57%)**
	ASTHMA	1 (1.79%)
	BRONCHIAL HYPERREACTIVIT	1 (1.79%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		**1 (1.79%)**
	ECZEMA	1 (1.79%)
TOTAL SUBJECTS WITH SAE		20 (54%)

7.3.3 Dropouts and/or Discontinuations

Of the three trials, PACTG 1021 had the highest frequency of discontinuation at 14% (6/43) as compared to PACTG 382 11% [11/102] and AI66922 5% [2/37] (see Table 21). Skin-related [6/182] and gastrointestinal AEs [5/182] were the most common cause of discontinuations over all the studies (3%).

Table 21: Discontinuations Related to AEs by Trial

		AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total (N=182)
Full name of the System Organ Class	Full name of the MedDRA Preferred Term	N (%)	N (%)	N (%)	N (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		**0 (0.00%)**	**1 (0.50%)**	**0 (0.00%)**	**1 (0.50%)**
	LYMPHADENITIS	0 (0.00%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
GASTROINTESTINAL DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**4 (3.9%)**	**5 (2.49%)**
	ABDOMINAL PAIN	0 (0.0%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
	DIARRHOEA	0 (0.0%)	1 (2.3%)	3 (2.9%)	4 (2.2%)
	LIP SWELLING	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
	NAUSEA	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		**1 (2.7%)**	**1 (2.3%)**	**1 (1.0%)**	**3 (1.49%)**
	PRODUCT TASTE ABNORMAL	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	PYREXIA	0 (0.0%)	1 (2.3%)	1 (1.0%)	2 (1.1%)
INVESTIGATIONS		**0 (0.00%)**	**0 (0.00%)**	**1 (1.0%)**	**1 (0.50%)**
	BLOOD GLUCOSE	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
METABOLISM AND NUTRITION DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**1 (1.0%)**	**2 (1.1%)**
	DECREASED APPETITE	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	DEHYDRATION	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (0.55%)
NERVOUS SYSTEM DISORDERS		**1 (2.7%)**	**0 (0.00%)**	**1 (1.0%)**	**2 (1.1%)**
	EPILEPSY	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (0.55%)
	SOMNOLENCE	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
PSYCHIATRIC DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**1 (1.0%)**	**2 (1.1%)**
	DECREASED ACTIVITY	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	THINKING ABNORMAL	0 (0.0%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**5 (4.9%)**	**6 (3.2%)**
	DERMATITIS ALLERGIC	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	ECZEMA	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	ERYTHEMA MULTIFORME	0 (0.0%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PRURITUS	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.55%)
	RASH	0 (0.0%)	1 (2.3%)	2 (2.0%)	3 (1.6%)
	RASH MACULO-PAPULAR	0 (0.0%)	0 (0.0%)	3 (2.9%)	3 (1.6%)
	URTICARIA	0 (0.0%)	0 (0.0%)	1 (1.0.%)	1 (0.55%)
TOTAL NUMBER OF DISCONTINUATIONS:		**2 (5.4%)**	**6 (14%)**	**11 (10.8%)**	**19 (10%)**

7.3.4 Significant Adverse Events

Adverse events of any grade were reported in all treated subjects (100%) and the majority of AEs were of Grade 1 or Grade 2 intensity. The most commonly reported (> 20%) clinical AEs were diarrhea (46%), acute otitis media (36%), upper respiratory tract infection (32%), cough (25%), pyrexia (25%), and vomiting (24%). The incidence of nervous system symptoms and rash were 12% and 36%, respectively.

Overall, Grade 3 to Grade 4 adverse events were more frequent in Studies PACTG 382 (23%) and PACTG 1021 (26%) than in study AI266922 (11%) [see Table 22].

Throughout the studies gastrointestinal AEs were the most frequent category of Grade 3-4 AEs (7.1% [13/182]), with diarrhea (2.2%[4/182]) making up the largest subset. The second most common category of Grade 3-4 AEs were blood and lymphatic AEs (6% [11/182]) with neutropenia (4% [8/182]) making up the largest subset. Overall, Grade 3-4 skin-related AEs were observed at a frequency of 4% with rash (2.7%) being the most common subset. Study AI266922 had only one Grade 3-4 skin-related AE of eczema.

Reviewer Comment: The decreased frequency of Grade 3-4 AEs in AI266922 as compared to PACTG 382 and PACTG 1021 may be related to decreased time of exposure in AI266922.

Table 22: Grade 3-4 Adverse Events by Trial

Full name of the System Organ Class	Full name of the MedDRA Preferred Term	AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	All Studies (N=182)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		**1 (2.7%)**	**1 (2.3%)**	**9 (8.8%)**	**11 (6.0%)**
	ANAEMIA	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	IDIOPATHIC THROMBOCYTOPENIC PURPURA	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	NEUTROPENIA	1 (2.7%)	1 (2.3%)	6 (5 9%)	8 (4.3%)
	THROMBOCYTOPENIA	0 (0.00%)	0 (0.00%)	2 (2 0%)	2 (1.1%)
GASTROINTESTINAL DISORDERS		**2 (5.4%)**	**4 (9.3%)**	**7 (6.9%)**	**13 (7.1%)**
	ABDOMINAL PAIN	0 (0.00%)	1 (2.3%)	2 (2 0%)	3 (1.6%)
	APHTHOUS STOMATITIS	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	CONSTIPATION	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	DENTAL CARIES	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	DIARRHOEA	1 (2.7%)	2 (4.7%)	1 (1 0%)	4 (2.2%)
	INTESTINAL PERFORATION	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
	PANCREATITIS	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	PROCTALGIA	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	VOMITING	0 (0.00%)	0 (0.00%)	2 (2 0%)	2 (1.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		**0 (0.00%)**	**3 (7.0%)**	**2 (2.0%)**	**5 (2.7%)**
	PAIN	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PYREXIA	0 (0.00%)	2 (4.7%)	2 (2 0%)	4 (2.2%)
HEPATOBILIARY DISORDERS		**0 (0.00%)**	**0 (0.00%)**	**1 (1.0%)**	**1 (0.55%)**
	HEPATOMEGALY	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		**0 (0.00%)**	**1 (2.3%)**	**0 (0.00%)**	**1 (0.55%)**
	BURNS SECOND DEGREE	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
METABOLISM AND NUTRITION DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**1 (1.0%)**	**2 (1.1%)**
	DEHYDRATION	0 (0.00%)	1 (2.3%)	1 (1 0%)	2 (1.1%)
NERVOUS SYSTEM DISORDERS		**0 (0.00%)**	**2 (4.7%)**	**0 (0.00%)**	**2 (1.1%)**
	DIZZINESS	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	HEADACHE	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
PSYCHIATRIC DISORDERS		**0 (0.00%)**	**1 (2.3%)**	**1 (1.0%)**	**2 (1.1%)**
	ABNORMAL DREAMS	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PSYCHOTIC DISORDER	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	THINKING ABNORMAL	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		**0 (0.00%)**	**0 (0.00%)**	**1 (1.0%)**	**1 (0.55%)**
	PENILE ADHESION	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		**1 (2.7%)**	2 (4.7%)	**3 (2.9%)**	**6 (3.3%)**
	BRONCHIAL HYPERREACTIVITY	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
	DYSPNOEA	0 (0.00%)	2 (4.7%)	0 (0.00%)	2 (1.1%)
	EPISTAXIS	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	OROPHARYNGEAL PAIN	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	RHINORRHOEA	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS **		**1 (2.7%)**	**3 (7.0%)**	**4 (3.9%)**	**8 (4.4%)**
	ECZEMA	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
	PRECANCEROUS SKIN LESION	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PRURITUS	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
	RASH	0 (0.00%)	2 (4.7%)	3 (2 9%)	5 (2.7%)
	RASH MACULO-PAPULAR	0 (0.00%)	0 (0.00%)	4 (3 9%)	4 (2.2%)
	ERYTHEMA MULTIFORME	0 (0.00%)	1 (2.3%)	1 (1.0%)	2 (1.1%)
VASCULAR DISORDERS		**0 (0.00%)**	**0 (0.00%)**	**1 (1.0%)**	1 (0.55%)
	DEEP VEIN THROMBOSIS	0 (0.00%)	0 (0.00%)	1 (1 0%)	1 (0.55%)
TOTAL GRADE 3-4		**4 (11%)**	**11 (26%)**	**23 (23%)**	**38 (21%)**

7.3.5 Submission Specific Primary Safety Concerns

Rash

With respect to rash events of special interest, the Applicant had to re-grade serious skin-related AEs like erythema multiforme (EM) for studies PACTG 382 and PACTG 1021 in which the investigators originally coded the lesions at a lower grade level (e.g. Grade 2) when the Division of AIDS AE grading table specifies EM or the presence of target lesions (which can be considered a manifestation of EM) as Grade 4. Reconciliation of the data by the Applicant's clinical review resulted in a total of 2 subjects with Grade 3 rash (confluent rash with fever, generalized rash), and 4 subjects with Grade 4 rash (all qualifying as erythema multiforme). The overall frequency of Grade 2-4 rashes was greater in Studies PACTG 382 (33% [34/102]) and PACTG 1021 (37% [16/43]) then Study AI266922 (8.1% [3/37]) [see Table 23]. In comparing the more concerning Grade 2-4 skin related AEs (e.g. rashes, macular-papular rash, urticaria, and erythema multiforme) between studies PACTG 382 and 1021, there were some differences such as a markedly increased maculopapular rash in PACTG 382 as compared to PACTG 1021 (11% versus 0%) but the overall the frequency of concerning rashes appear to be similar. Study AI266922 had no concerning Grade 2-4 skin-related AEs. Overall, there was no difference in skin-related AE frequency for those subjects younger than three years and those three years and older.

Table 23: Comparison of Grade 2-4 Rash AE

Full name of the MedDRA Preferred Term	AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total (N=182)
BLISTER	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
DERMATITIS	0 (0.00%)	0 (0.00%)	2 (2.0%)	2 (1.00%)
DERMATITIS ALLERGIC	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
DERMATITIS ATOPIC	1 (2.7%)	0 (0.00%)	1 (1.0%)	2 (1.00%)
DERMATITIS CONTACT	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
DERMATITIS DIAPER	0 (0.00%)	2 (4.7%)	4 (3.9%)	6 (3.3%)
DERMATOSIS	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
ECZEMA	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
ERYTHEMA	0 (0.00%)	0 (0.00%)	2 (2.0%)	2 (1.00%)
ERYTHEMA MULTIFORME	0 (0.00%)	1 (2.3%)	3 (2.9%)	4 (2.2%)
ERYTHEMA NODOSUM	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
LIPOATROPHY	1 (2.7%)	0 (0.00%)	0 (0.00%)	1 (0.55%)
PAPULE	0 (0.00%)	1 (2.3%)	1 (1.0%)	2 (1.00%)
PRECANCEROUS SKIN LESION	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
PRURITUS	0 (0.00%)	2 (4.7%)	2 (2.0%)	4 (2.2%)
RASH	0 (0.00%)	8 (19%)	16 (16%)	24 (13%)
RASH ERYTHEMATOUS	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
RASH GENERALISED	0 (0.00%)	2 (4.7%)	0 (0.00%)	2 (1.00%)
RASH MACULO-PAPULAR	0 (0.00%)	0 (0.00%)	11 (11%)	11 (6.0%)
RASH PAPULAR	0 (0.00%)	1 (2.3%)	3 (2.9%)	4 (2.2%)
RASH PRURITIC	0 (0.00%)	0 (0.00%)	2 (2.0%)	2 (1.00%)
SEBORRHOEA	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.50%)
SKIN HYPERPIGMENTATION	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.50%)
SKIN LESION	0 (0.00%)	2 (4.7%)	0 (0.00%)	2 (1.00%)
SKIN REACTION	0 (0.00%)	0 (0.00%)	3 (2.9%)	3 (1.6%)
SKIN ULCER	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
SWELLING FACE	0 (0.00%)	2 (4.7%)	1 (1.0%)	3 (1.6%)
URTICARIA	0 (0.00%)	0 (0.00%)	1 (1.0%)	1 (0.55%)
TOTAL Grade 2-4	3 (8.1%)	16 (37%)	34 (33%)	53 (29%)

Neuropsychiatric AEs

The overall incidence of the Grade 2-4 neurologic events in Studies PACTG 382 and PACTG 1021 was similar (11% [11/102]and 14% [6/43], respectively), but was lower in Study AI266922 (8.1% [3/37]) [see Table 24]. In adults, limited data suggest that patients receiving EFV could be at increased risk for seizures, especially when there is a known medical history of seizures. A total of 3 subjects experienced a seizure event while on EFV. Two were reported as febrile seizures and the third was attributed to congenital toxoplasmosis. In regard to Grade 2-4 psychiatric AEs, Studies PACTG 1021 (7.0% [3/43]) had more subjects with Grade 2-4 AEs than PACTG 382 (2.9% [3/102]). Although there were no psychiatric AEs with more than one subject affected, the types of AEs (e.g. abnormal dreams, insomnia, depression, and psychotic behavior) were consistent with EFV AEs reported in adults. In analysis by age subgroups, the overall incidence of selected neurologic events (all Grades) was lower in subjects < 3 years old than in subjects ≥ 3 years old (5% [3/61] vs. 22% [26/121], respectively), with no reports of relevant psychiatric disorders in the < 3 years group [see Table 25]

Reviewer Comments: It appears that older children report more events of relevant psychiatric disorders, possibly reflecting experiences specific to adolescence. Conversely, there may be under-reporting of such events in younger children who may not verbally identify these experiences. Indeed, in an analysis by age subgroups, the overall incidence of selected neurologic events was lower in subjects < 3 years than in subjects ≥ 3 years (5% vs. 22%).The Applicant has also updated the warning in the EFV label concerning use of EFV in those at risk for seizures should be extended to include pediatric patients.

Table 24: Comparison of Grade 2-4 Neuropsychiatric AEs

Full name of the System Organ Class	Full name of the MedDRA Preferred Term	AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total
NERVOUS SYSTEM DISORDERS		**3 (8.1%)**	**6 (14%)**	**11 (11%)**	**20 (11%)**
	BALANCE DISORDER	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	CONVULSION	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	DISTURBANCE IN ATTENTION	0 (0.00%)	0 (0.00%)	1 (0.98%)$	1 (0.55%)
	DIZZINESS	0 (0.00%)	1 (2.3%)	1 (0.98%)	2 (1.1%)
	FEBRILE CONVULSION	2 (5.4%)	0 (0.00%)	0 (0.00%)	2 (1.1%)
	HEADACHE	1 (2.7%)	2 (4.7%)*	6 (5.9%)	9 (5.0%)
	HYPERTONIA	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	HYPOREFLEXIA	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	HYPOTONIA	0 (0.00%)	1 (2.3%)	1 (0.98%)	2 (1.1%)
	MUSCLE SPASTICITY	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PSYCHOMOTOR HYPERACTIVITY	0 (0.00%)	0 (0.00%)	1 (0.98%)	1 (0.55%)
	SINUS HEADACHE	0 (0.00%)	0 (0.00%)	1 (0.98%)	1 (0.55%)
	SOMNOLENCE	0 (0.00%)	0 (0.00%)	1 (0.98%)#	1 (0.55%)
	SYNCOPE	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
PSYCHIATRIC DISORDERS		**0**	**3 (7.0%)**	**3 (2.9%)**	**6 (3.3%)**
	ABNORMAL DREAMS	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	DECREASED ACTIVITY	0 (0.00%)	0 (0.00%)	1 (0.98%)#	1 (0.55%)
	DEPRESSION	0 (0.00%)	1 (2.3%)*	0 (0.00%)	1 (0.55%)
	DYSPHEMIA	0 (0.00%)	0 (0.00%)	1 (0.98%)	1 (0.55%)
	INSOMNIA	0 (0.00%)	1 (2.3%)*	0 (0.00%)	1 (0.55%)
	NIGHTMARE	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
	PSYCHOTIC BEHAVIOUR	0 (0.00%)	0 (0.00%)	1 (0.98%) $	1 (0.55%)
	PSYCHOTIC DISORDER	0 (0.00%)	0 (0.00%)	1 (0.98%) $	1 (0.55%)
	THINKING ABNORMAL	0 (0.00%)	1 (2.3%)	0 (0.00%)	1 (0.55%)
Grand Total		**3 (8.1%)**	**8 (19%)**	**12 (12%)**	**23 (13%) *#$**

* In study PACTG1021, subject 460986 had both neurological AE (headache) and psychological AE (depression and insomnia)
# In study PACTG382, subject 380343 had both neurological AE (somnolence) and psychological AE (decreased activity)
$ In study PACTG382, subject 650403 had both neurological AE (disturbance in attention) and psychological AE(s) (psychotic disorder and behaviors)

Table 25: Neurologic Adverse Events of Special Interest (all Grades) by Age-Treated Subjects (Studies PACTG 382, PACTG 1021, AI266922)

System Organ Class Preferred Term	Number of Subjects (%)		
	Age Group		
	AGE < 3 YEARS N=61	AGE >= 3 YEARS N=121	TOTAL N=182
ANY ADVERSE EVENT	3 (4.9%)	26 (22%)	29 (16%)
NERVOUS SYSTEM DISORDERS	3 (4.9%)	16 (13%)	19 (10%)
DIZZINESS	1 (1.6%)	10 (8.3%)	11 (6.0%)
SOMNOLENCE	0	4 (3.3%)	4 (2.2%)
BALANCE DISORDER	0	3 (2.5%)	3 (1.6%)
PSYCHOMOTOR HYPERACTIVITY	0	2 (1.7%)	2 (1.1%)
ATAXIA	1 (1.6%)	0	1 (0.5%)
DISTURBANCE IN ATTENTION	0	1 (0.8%)	1 (0.5%)
LETHARGY	1 (1.6%)	0	1 (0.5%)
PSYCHIATRIC DISORDERS	0	12 (9.9%)	12 (6.6%)
INSOMNIA	0	6 (5.0%)	6 (3.3%)
NIGHTMARE	0	5 (4.1%)	5 (2.7%)
DEPRESSION	0	3 (2.5%)	3 (1.6%)
ABNORMAL DREAMS	0	2 (1.7%)	2 (1.1%)
MAJOR DEPRESSION	0	1 (0.8%)	1 (0.5%)
SLEEP DISORDER	0	1 (0.8%)	1 (0.5%)
THINKING ABNORMAL	0	1 (0.8%)	1 (0.5%)

Table 25 adapted from Applicant's Summary of Clinical Safety Table 2.3.1.B

Hepatic Related AEs and Laboratory Abnormalities:
In PACTG 382, PACTG 1021 and AI266922, no subject met Hy's Law criteria for drug-related liver toxicity. Only one subject in PACTG 1021 had a Grade 3 total bilirubin. The incidence of Grade 3-4 transaminase abnormalities was no greater than 5% in any one study [see Table 26]. Study PACTG 1021 and PACTG 382 had similar frequencies of Grade 3-4 transaminase abnormalities (5% [2/43] versus 5% [5/102], respectively) with AI266922 have a lower frequency of 3% [1/37]. No liver failure or ascites reported in any of the studies.. However there were nine subjects in Study PACTG 382 with hepatomegaly: four with Grade 1, four with Grade 2, one with Grade 3 (see Table 22 above). In Study PACTG 1021, there was one subject with a Grade 2 hepatomegaly and one subject with cholelithiasis (ungraded). In Study AI266922, there was one subject with Grade 1 hepatosplenomegaly.

Table 26: Grade 3-4 ALT or AST

Lab Test Name	DAIDS Highest On-Trt Tox Grade	AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total (N=182)
Alanine Aminotransferase (ALT)	**3**	1 (2.7%)	0 (0.00%)	3 (2.9%)	4 (2.2%)
	4	0 (0.00%)	1 (2.3%)	2 (2.0%)	3 (1.6%)
Aspartate Aminotransferase (AST)	**3**	0 (0.00%)	2 (4.6%)	0 (0.00%)	2 (1.1%)
	4	0 (0.00%)	0 (0.00%)	2 (2.0%)	2 (1.1%)
TOTAL Grade 3-4 ALT or AST		**1 (2.7%)**	**2 (4.6%)**	**5 (4.9%)**	**7 (3.8%)**

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Excluding Investigations (laboratory) AEs, the most common AEs (>20% in any group and all grades of severity) in all three major pediatric studies included infections such as pneumonia, gastroenteritis, and impetigo. Diarrhea, vomiting, rash, cough, and pyrexia [were also common AEs.

7.4.2 Laboratory Findings

Across the three studies, approximately 35-41% [AI266922 (13/37) or PACTG 1021 (15/43); PACTG 382 (42/102)] of subjects had Grade 3-4 laboratory abnormalities (see Table 27). Neutropenia was the most common Grade 3-4 abnormality with 26-31% of subjects in PACTG 382 and PACTG 1021 [PACTG 1021 (11/43) and PACTG 382 (32/102)] and 14% [5/37] of subjects in AI266922. The next most common Grade 3-4 abnormality was a high ALT or AST observed in 5% - 7% of subjects in PACTG 382 and PACTG 1021[PACTG 382 (5/102) and PACTG 1021 (3/43)], respectively, but none in AI266922. Hypoglycemia was observed in 4% - 5% of subjects in PACTG 382 and PACTG 1021 but in no subjects in AI266922.

Reviewer Comment: The frequency of common laboratory abnormalities such as neutropenia and elevated AST or ALT were less common in Study AI266922 than in the other two trials. The Applicant explains this by emphasizing that subjects in Study AI266922 had a shorter overall exposure to drug and therefore fewer laboratory abnormalities. Note: Subject 00008 in Study AI266922 had indications of pancreatitis by laboratory values but did not have an AE listed for pancreatitis nor was there a narrative.

Table 27: Grade 3-4 Laboratory Values Across Studies

	AI266-922 (N=37)	PACTG1021 (N=43)	PACTG382 (N=102)	Total (N=182)
Low Hemoglobin	1 (2.7%)	0	2 (2.0%)	3 (1.6%)
Low Neutrophils	5 (14%)	11 (26%)	32 (31%)	48 (26%)
Platelets low	0	0	2 (2.0%)	2 (1.1%)
Low Albumin	0	0	3 (2.9%)	3 (1.7%)
High ALT	0	1 (2.3%)	5 (4.9%)	6 (3.3%)
High AST	0	2 (4.6%)	2 (2.0%)	4 (2.2%)
Either High AST or High ALT	0	3 (7.0%)	5 (4.9%)	8 (4.4%)
High Total Bilirubin	0	1 (2.3%)	0	1 (0.55%)
High LDL	0	0	3 (2.9%)	3 (1.6%)
High Triglycerides	0	0	1 (1.0%)	1 (0.55%)
High Amylase	4 (11%)*	0	0	4 (2.2%)
Total Lipase	1 (2.7%)*	0	0	1 (0.55%)
Low Sodium	1 (2.7%)	0	0	1 (0.55%)
High Sodium	0	0	1 (1.0%)	1 (0.55%)
High Potassium	0	0	1 (1.0%)	1 (0.55%)
Low Bicarbonate	1 (2.7%)	0	1 (1.0%)	2 (1.1%)
High Creatinine	0	0	1 (1.0%)	1 (0.55%)
Low Glucose	0	2 (4.7%)	4 (3.9%)	6 (3.3%)
High Alkaline Phosphatase	1 (2.7%)	1 (2.3%)	2 (2.0%)	4 (2.2%)
High LDH	2 (5.4%)	0	0	2 (1.1%)
TOTAL Grade 3-4	**13 (35%)**	**15 (35%)**	**42 (41%)**	**70 (38%)**

* Subject 00008 had Grade 3 amylase and a Grade 4 lipase

7.4.3 Vital Signs

Vital signs and physical examinations were conducted at protocol-defined visits in the 3 studies, and investigators could report abnormalities observed as AEs, if appropriate. In Studies PACTG 382 and PACTG 1021, no formal analyses of vital signs or physical examination results were conducted. No significant reports of an AE associated with a vital sign in absence of another AE process like a respiratory infection.

7.4.4 Electrocardiograms (ECGs)

ECGs were not conducted in any of the 3 key pediatric studies (PACTG 382, PACTG 1021, and AI266922)

7.5 Other Safety Explorations

Sixth Status Report for Liquid Expanded Access Program LEAP Studies and Named Patient Programs for HIV-1 infected individuals failing or intolerant of their current antiretroviral (ARV) regimen who were able to take oral liquid medications, but were unable to swallow capsules and who had no other satisfactory therapeutic options without the EFV oral solution,

(Data for Studies AI266802/AI266803/AI266913/AI266914/AI266916 combined)

Enrollment: There were sixty-six sites enrolled subjects. Overall, 145 pediatric subjects were enrolled, and 129 were treated with EFV.

Disposition: As of the cutoff date for this report, 3 of 145 enrolled pediatric subjects (2%) are still continuing on treatment (see Table 26). The most common reason for discontinuation of study drug was for “other” reasons, mostly requests to switch to EFV capsules (31 of 46 subjects).

Safety Findings (see Table 28):
The LEAP studies had a similar frequency of adverse events as that observed in the three controlled studies in this submission. There were two deaths due to Hodgkin’s Lymphoma and advanced HIV disease (see Appendix Section 9.4). Many of the SAEs and the discontinuations were related to infections and complications of advanced HIV disease. The frequencies of rash and neuropsychiatric AEs were also similar to the three controlled studies in this submission.

Table 28: Safety of Treated Pediatric Subjects

System Organ Class Preferred Term	No. of Subjects (%) N = 129
Deaths	2 (1)
Serious Adverse Events	11 (9)
Discontinuations Due to Adverse Events	18 (14)
Any Adverse Event	62 (48)
Most Common Adverse Events (≥ 5% of Subjects):	
Rash	13 (10)
Vomiting	13 (10)
Diarrhea	11 (9)
Otitis Media	10 (8)
Pyrexia	9 (7)
Pneumonia	7 (5)
Sinusitis	6 (5)
Adverse Events of Special Interest	
Rash	22 (17)
Rash	13 (10)
Urticaria	4 (3)
Rash Papular	2 (2)
Rash Erythematous, Rash Macular, Rash Maculo-papular, Skin Irritation, Skin Lesion	1 (< 1) each
Nervous System Events	9 (7)
Insomnia	5 (4)
Nightmare	3 (2)
Cognitive Disorder, Depression, Hallucination	1 (< 1) each

7.6.3 Pediatrics and Assessment of Effects on Growth

Height, weight and body surface area were followed. Effective treatment of HIV has been repeatedly shown to improve growth of HIV infected children. Other than isolated reports of growth failure, there was no consistent concern about growth in the three major trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was a single overdose case in Study PACTG 382 that was listed as an SAE:

The almost 4 year old subject initiated therapy with EFV 250 mg, NFV 1500 mg, ZDV 200 mg, and 3TC 130 mg daily on 03-Nov-1997 (Day 1). On 13-Nov-1997 (Day 11), the subject presented with rash with about 50-70 2-5 mm slightly flat lesions on trunk and limbs. His rash had many macules and flat papules with minimal pruritus. The event of rash was judged by the investigator to be moderate (Grade 2) and definitely related to the study medication. He was treated with hydroxyzine and Aveeno®. The rash was almost gone in 24 hrs, with residual telangiectatic areas. The event rash was considered resolved on 21-Nov-1997 (Day 19). Study medication was continued unchanged for this event. On 07-Aug-1998 the subject had diarrhea which was treated with Pepto Bismol®. The diarrhea resolved on 30-Aug-1998. On 27-Aug-1998 (Day 298), the subject experienced an overdose. The event of overdose was judged by the investigator to be mild (Grade 1). On 10-Sep-1998, it was discovered that the grandmother gave EFV 100 mg tabs BID for the previous 2 weeks. She was "re-instructed on the correct dose." The investigator assessed the diarrhea as possibly related to EFV..

7.7 Additional Submissions / Safety Issues

A 90-day safety update was received from the Applicant on February 1, 2013.
Since the data cutoff date for the Safety Clinical Summary (SCS) (08-Feb-2012) through the data cutoff date for this 90-day safety update (18-Oct-2012), the following new safety observations from Study AI266922 are available:

- No new deaths, SAEs, or discontinuations due to AEs have been reported.
- Ten subjects have reported AEs (all < 3 years at study entry). All AEs were Grade 1, except for 3 AEs (Grade 2 viral upper respiratory tract infection and febrile convulsion in Subject AI266922-27-49 and Grade 2 viral upper respiratory tract infection in Subject AI266922-27-53). All AEs were considered not related to the study drug by the investigators, except for the febrile convulsion in Subject AI266922-27-49

- Events of special interest:
  - Grade 2 febrile convulsion that occurred on Day (b) (6) was reported in Subject AI266922-27-49. This subject was < 3 years of age. The AE was considered not likely related to the study drug by the investigator and resolved the same day. This subject had previously had Grade 2 febrile convulsion on Day (b) (6) that was considered not likely related to the study drug by the investigator and resolved the same day.

  - Six subjects had rash events of special interest. Five of these subjects had previously reported rash events of special interest. Therefore, the overall incidence of rash events of special interest increased from 8 subjects (22%), as reported in the Summary of Clinical Safety, to 9 subjects (33%) with the addition of 1 more subjects from Study AI266922.

  - No subjects reported events of liver toxicity or drug-induced liver injury.

- Few new laboratory abnormalities, and no new Grade 3 - 4 laboratory abnormalities, have been reported.

8 Postmarket Experience

To supplement the clinical trial safety data presented in this summary, a search of the Applicant's Corporate Adverse Event Reporting System (CARES) database was conducted to ensure the inclusion of all available safety data for children in the 3 month to 3 year age range, since this is the group for which an extension of indication is sought. The cumulative search covered all EFV reports received through 2-May-2012. In order to avoid duplication of data, the Applicant's search excluded cases reported from Studies PACTG 382, PACTG 1021, and AI266922. Otherwise, the search included all reports from studies other than these 3 key pediatric studies, as well as all spontaneous reports, and all literature-derived reports. Results identified 13 unique cases, including 3 cases of events of special interest for EFV (1 each of rash, insomnia, and increased transaminases). The remaining 10 cases included a majority of infection-related events (n=6; 5 from South Africa and 1 from Thailand), consisting of 2 lower respiratory tract infections, 1 pneumonia, 1 pulmonary tuberculosis (TB), 1 fatal sepsis in association with diarrhea, and 1 case of herpes zoster pneumonia that resolved with acyclovir treatment. The remaining 4 reports included 1 each of urticaria and bronchospasm, both of which resolved apparently without sequellae, 1 accidental exposure (without sequellae), and 1 case of Guillain-Barre Syndrome (GBS) that had complete resolution after 4 weeks. In 3 of the 13 cases, immune reconstitution syndrome was invoked as a probable complicating factor (herpes zoster pneumonia, pneumonia, and GBS). Five of the 10 reports came from non-BMS studies (4 from a single study in South Africa, including the 2 lower respiratory tract infection cases, the pneumonia case, and the herpes zoster case; and the single pulmonary TB case was from another study in Africa). Two of the 13 reports were derived from the literature (the fatal sepsis with diarrhea case and the GBS case).

With respect to the 3 events of special interest, the rash was reported as being maculo-papular in character, involving the entire body and associated with "pink eyes and swollen lips" as well as pyrexia; onset was 1.5 weeks after initiation of therapy. Resolution occurred rapidly over the week following discontinuation of therapy, and involved desquamation.

Reviewer Comment: This case could have been a case of Steven-Johnsons syndrome; however, no additional clarifying information was available for this post-marketing case.

The case of insomnia occurred in a 2-year-old and resolved when dosing was adjusted to administer EFV in the morning instead of the evening. The transaminitis report provided very limited information, but interruption of drug was associated with resolution, and hepatitis A serology was positive, although the temporal relationship of the serology to the event was not clear. In summary, the review of these 13 incremental reports from the CARES database indicated that all cases were consistent with the types of clinical events

already documented in the 3 clinical study datasets presented in this submission for children in the age range of 3 months to 3 years, and with the overall existing safety profile of EFV in older children and adults.

9 Appendices

9.1 Literature Review/References

Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects in Adult AIDS Clinical Trial Group study. AIDS 2004;18:2391-2400.

9.2 Labeling Recommendations

The following labeling changes below (in track changes) by section were recommended to the Applicant by the review team. We are working with patient labeling team to revise the instructions for capsule sprinkle section of the PPI.

(b) (4)

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

(b) (4)

9.4 Narratives

Death Narratives for PACTG 382

Patient Identifier: PACTG382-6704-500082 (Cohort I)

Prior Study Medication through Day 146
Efavirenz (EFV)Capsules/Tablet 250 mg
Nelfinavir (NFV) Capsule/Tablets 1500 mg
Stavudine (d4T) Capsule/Tablets 40 mg

Medication Start Date: 04-Nov-1997
Age: 7.9 years
Gender: Male **Race:** White **Ethnicity:** N/A
General Medical History: Information not provided
Baseline At time of event
Value
Test: Study Day (Absolute) (%) Study Day (Absolute) (%)
Day 1 CD4 count: 915 cells/mm^3 39%
Day 14: CD4 count: 850 cells/mm^3 22%
Day 1 HIV Viral load: 556,000 copies/mL
Day 14 HIV Viral load: 3,346 copies/mL
Concomitant Medication(s):
None
Prior Antiretroviral Therapy:
Zidovudine (07-Apr-1990-20-Sep-1995), (12-Jun-1997-04-Nov-1997)
Didanosine (16-Feb-1995-23-Jun-1997)
Lamivudine (12-Jun-1997-04-Nov-1997)

Other Post Randomization Adverse Events (day of onset): Alanine aminotransferase increased (Day 1, 113, 147), aspartate aminotransferase increased (Day 1, 57, 113, 147), rash (Day 13, 111, 177), blood alkaline phosphatase increased (Day 28, 84, 113), blood glucose increased (Day 84), blood sodium increased (Day 84, 113, 147), blood potassium increased (Day 113), hemoglobin decreased (Day 512),neutrophil count decreased (Day 512), pneumonia (Day (b) (6)), staphylococcal sepsis (Day (b) (6)), Hodgkin's disease Stage IV (Day (b) (6)), aspiration (Day 536), death (Day (b) (6)).

Clinical Summary
The subject initiated therapy with EFV 250 mg, NFV 1500 mg and d4T 40 mg daily on 04-Nov-1997 (Day 1). On 16-Nov-1997 (Day 13), the subject presented with rash on

trunk, face and limbs. This was judged by the investigator to be moderate (Grade 2) and probable/possibly related to the study medication. The subject had chronic and recurrent atopic dermatitis with diffuse patchy erythematous rash. On 22-Feb-1998 (Day 111), the event of rash improved to mild (Grade 1) intensity and was considered resolved on 30-Mar-1998 (Day 147). On 29-Apr-1998 (Day 177), he again presented with rash which was judged by the investigator to be mild (Grade 1). The event rash was considered resolved on 14-Sep-1998 (Day 315). Subject died of staphylcoccal sepsis more than (b) (6) after the last dose of study medication (b) (6)

Death Narratives for AI266922:
Pre-Treatment AI266922 Deaths:

Subject Identifier: AI266922-4-39
Event: Pneumonia, Grade 4 and Death
Study Medication: Efavirenz **Starting Dose:** N/A
Treatment Group: N/A **Date of First Dose:** N/A
Age: 5 months **Gender:** Female **Race:** White **Ethnicity:** N/A
Disease History: N/A
Significant Medical History: None
Relevant Concomitant Medication(s): None
Clinical Summary:
This subject was a 5 month-old white female who had pneumonia at screening and died prior to the initiation of study therapy. The subject was treated with amoxicillin/clavulanate for an unspecified reason from (b) (6). She presented on (b) (6) with respiratory distress and râles on physical examination, and was hospitalized with a diagnosis of pneumonia commencing on (b) (6). She was treated with intravenous fluids, unspecified antimicrobial drugs and oxygen. She was screened for the study on 16-Jul-2008. Her condition worsened and she was transferred to intensive care on an unknown date. She died of septic shock on (b) (6). The investigator considered the event to be not related to the study medication, which was never initiated.

Subject Identifier: AI266922-19-27
Event: Sepsis, Grade 4, Death
Study Medication: Efavirenz
Treatment Group: N/A **Date of First Dose:** N/A
Age: 4 months **Gender:** Female **Race:** White **Ethnicity:** N/A
Disease History: N/A
Significant Medical History: N/A
Relevant Concomitant Medication(s): N/A
Clinical Summary:
This subject was a 4 month-old white female who developed sepsis and died prior to the institution of study therapy. She was screened on 27-Nov-2007 and returned to the

clinic on (b) (6) in poor condition with hematemesis, mydriasis, anisocoria, and lower extremity cyanosis. She did not respond to cardiopulmonary resuscitation and died that (b) (6). Death was attributed to sepsis. No autopsy was reported. Study therapy was never initiated and the investigator considered the event to be unrelated to the study medication.

On Treatment AI266922 Deaths:

Subject Identifier: AI266922-27-51
Event: Gastritis, Grade 2, Not related, Day - (b) (6)
Esophageal candidiasis, Grade 3, Not related, Day - (b) (6)
Dehydration, Grade 4, Not related, Day - (b) (6)
Gastroenteritis, Grade 4, Not related, Day - (b) (6)
Gastroenteritis, Grade 2, Not likely related, Day (b) (6)
Bacterial infection, Grade 4, Not related, Day (b) (6)
Reason(s) for Narrative: X Death x SAE
Study Medication: Efavirenz **Starting Dose:** 300 mg capsule sprinkle
Treatment Group: N/A **Date of First Dose:** 29-Oct-2010
Age: 3 months **Gender:** Female **Race:** Black/African American **Ethnicity:** N/A
Disease History: Maternal/fetal transmission
Significant Medical History: Bacterial sepsis (hospitalized (b) (6))
Relevant Concomitant Medication(s): None

Clinical Summary:
This subject was a 3 month-old black/African American female with a prior history of bacterial sepsis who was hospitalized for gastritis (b) (6) days prior to the initiation of study therapy. She was screened for the study on 16-Sep-2010. On (b) (6) she was hospitalized with a 3-day history of hematemesis, and was diagnosed with gastritis. On admission she was not acutely ill and a “septic screen” was normal. Laboratory tests showed a white blood cell (WBC) count of 11.6 x 109 c/L (reference range: 5.5-18.0), hemoglobin (HGB) 9.8 g/dL (reference range: 10.0-15.0), platelet count 442 x 109 c/L (reference range: 140-350), C-reactive protein (CRP) 1.3 mg/L (reference range: 0.0- 5.0), potassium (K) 3.7 mmol/L (normal range 4.1-5.3), and negative cytomegalovirus IgG and IgM; blood chemistries were otherwise normal. The subject’s oral intake was restricted and she was treated with intravenous (IV) ampicillin and gentamicin, sulfamethoxazole/trimethoprim (SMZ-TMP), vitamin K, omeprazole and acetaminophen. Due to miscommunication, her highly active antiretroviral therapy (HAART) was not given. Her condition improved and she was reported to be eating well without further vomiting. On (b) (6), the gastritis was reported resolved and the subject was discharged home on omeprazole, SMZ-TMP, HAART, and multivitamins. No action was taken with regard to the study therapy, which had not yet been initiated. The investigator considered the event to be unrelated to the study medication, which had not yet been initiated. On (b) (6) the subject was hospitalized again with a 4-day history of loose stools and fever, and a 1-day

history of cough and vomiting which was being treated with amoxicillin/ clavulanate. She had unspecified clinical signs of lower respiratory infection, severe dehydration and hypovolemic shock, and was reported to have gastroenteritis and dehydration. Laboratory tests showed an arterial blood gas (ABG) with a pH of 7.16, pO2 68 mmHg, and pCO2 16 mmHg; WBC 9.9 x 109 c/L, HGB 6.9 g/dL, platelets 394 x 109 c/L, CRP 6.1 mg/L, creatinine 145 µmol/L (normal range 14-34), urea 17.4 mmol/L (normal range 1.4-5.0), K 3.1 mmol/L, and normal glucose. Stool examination revealed very scanty neutrophils and yeast cells, lymphocytes at 2.07 x 10E9/l (21.0%). Stool microscopy suggested an inflammatory process with scanty WBC and yeast; no red cells or parasites were seen. Blood cultures initially revealed gram positive cocci and subsequently grew *Enterococcus fecalis*. Stool culture was negative for enteric pathogens. The subject was given fluids via an intra-osseus line, her oral intake was restricted, and she given IV bicarbonate, cefotaxime, omeprazole, packed red cells, and continued HAART. Shortly after admission, the subject passed 'currant-jelly' stools and a pediatric surgeon was consulted for possible intussusception. Abdominal Xrays were negative for bowel obstruction. Her subsequent stools were melanotic. Over the next 12 hours her volume status improved, but she continued to have hematemesis. Gastroscopy on (b) (6) showed severe candida esophagitis with contact bleeding; she was reported to have esophageal candidiasis and IV fluconazole was added. The subject responded well, and oral feeding was slowly re-introduced. Her diarrhea, melena and hematemesis resolved completely and the gastroenteritis, dehydration, and esophageal candidiasis were all reported resolved on 18-Oct-2010 (Day -11). She was discharged on (b) (6) on oral abacavir, lamivudine, lopinavir + ritonavir, SMZ/TMP, fluconazole, and multivitamins, and topical zinc, castor oil, and nystatin cream for the diaper area. No action was taken with regard to the study therapy, which had not yet been initiated. The investigator considered these events to be not related to the study medication, which had not yet been initiated.

Study therapy was initiated on 29-Oct-2010.

On (b) (6) the subject presented with fever, vomiting, inability to tolerate oral intake and signs of dehydration. Gastroenteritis was diagnosed and she was hospitalized. Laboratory tests showed a sodium of 138 mmol/L (normal range: 135-147), potassium 3.9 mmol/L (normal range: 4.1- 5.3), chloride 115 mmol/L (normal range: 99-113), carbon dioxide < 5 mmol/L (normal range: 18-29), CRP 14.9 mg/L and urea 14.3 mmol/L. Chest X-ray was normal. Treatment with IV fluids and antibiotics was administered. The subject responded well and she was discharged with the gastroenteritis resolved on (b) (6) Study therapy was not interrupted. The investigator considered the gastroenteritis to be not likely related to the study medication.

On (b) (6) the subject died unexpectedly at home. She had been febrile the previous day, and was lethargic and ate poorly that morning. The parents did not seek medical attention and no treatment was reported. A bacterial infection was suspected. No action was taken with regard to the study therapy. The investigator considered the bacterial infection to be not related to the study medication.

Patient Identifier: AI266922-5-20
Event: Pneumonia, Grade IV, Not related to study drug, Day (b) (6)
Reason(s) for Narrative: X Death X SAE
Study Medication: Efavirenz **Dose:** *390 mg oral solution*
Treatment Group: N/A **Date of First Dose:** 14-Nov-2007
Age: 2 **Gender:** Female **Race:** White **Ethnicity:** N/A
Disease History: The subject was diagnosed with HIV on 27-Sep-2007; *Maternal/fetal transmission*
General Medical History: Oral candidiasis, diarrhea, cervical adenomegaly, seborrheic dermatitis, failure to thrive
Relevant Concomitant Medication(s): Nitrofurantoin, paracetamol, Histiacil nf (dextromethorphan/ambroxil), multivitamin, iron, ibuprofen, Caltusine
Clinical Summary:
2 y/o white female on EFV/ddI/FTC began to have productive cough on 01-Aug-2008 (Day 262 of treatment). On 10-Aug-2008 (Day 271), the subject received nebulizer treatment and amoxicillin for treatment of 'quick breathing'. On 13-Aug-2008 (Day 274), the subject experienced tachypnea and on (b) (6) she came to the hospital emergency room. The subject's vital signs showed respiratory rate as 30/min, heart rate as 100/min, blood pressure as 100/65, and temperature of 36 degrees Celsius. During physical examination, expiratory wheezes were noted. A physical examination and complete blood count did not support a bacterial infection and chest x-ray showed reticular infiltration. Hand ultrasonography ordered because of L hand edema showed subcutaneous tissue inflammation. Nebulizer treatment was repeated, observed for a few hours and was discharged with a diagnosis of laryngotracheitis. She received dicloxacillin due to the inflammatory process of the hand. *Caltusine (mucolytic/anti-tussive) therapy was added on 20-Aug-2008 (Day 281).* On (b) (6) , the subject was found prostrated and was taken to another hospital where she was intubated *due to respiratory failure*. Therapy with efavirenz, didanosine and emtricitabine was stopped on (b) (6) The subject died on (b) (6) due to pneumonia.

Death Narratives for LEAP Studies

Subject Identifier: AI266803-9-9005 (Death: Cardiomyopathy; Hodgkin's Disease); Serious Adverse Events: Cardiomyopathy; Hodgkin's Disease; Death

This 8-year-old ARV-experienced female began treatment on 28-Mar-2001, as she was being treated for *Mycobacterium avium-intracellulare* (MAI) with rifabutin and amikacin, and was unable to swallow. On (b) (6) , she was transferred to another hospital to receive chemotherapy for Hodgkin's lymphoma. She continued in the study.

She tolerated the first course of chemotherapy, but subsequently died on (b) (6) secondary to AIDS-related cardiomyopathy.

Significant medical history included cardiomyopathy, MAI, and Hodgkin's disease. ARV medication while on study included EFV, didanosine, and stavudine. Prior ARVs included lamivudine, abacavir, nevirapine, and nelfinavir.

Laboratory values on 21-Mar-2001 were HIV-1 RNA of 650,000 copies/mL and CD4 count of < 25 cells/mm3.

The physician and Applicant considered these events unlikely related to the study medication.

Subject Identifier: AI266803-36-36002 (Death: HIV Wasting Syndrome)
Serious Adverse Events: HIV Wasting Syndrome; Death

This 8-year-old ARV-naive female, with a history of severe wasting secondary to AIDS, began treatment on 30-Mar-2002. She received EFV oral solution 270 mg via nasogastric tube in combination with lamivudine 150 mg and abacavir 300 mg twice daily. She died on (b) (6).

Medical history included severe HIV wasting syndrome. Concomitant medications included rifampicin, pyrazinamide, amikacin, ethambutol, meropenem, isoniazid, and amphotericin.

Laboratory values on 08-Mar-2002 were HIV-1 RNA of 7,500,000 copies/mL and CD4 count of 10 cells/mm3.

The physician and Applicant considered these events not likely related to the study medication.

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/s/

ALAN M SHAPIRO
04/08/2013

GUOXING SOON
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Sign or Fraser

MARY E SINGER
04/08/2013
I concur with Dr. Shapiro and Smith's clinical-statistical review.