CLINICAL PHARMACOLOGY REVIEW

NDAs	20972/21360
Supplement Number	043/031
Submission Date	Nov 2, 2012
Brand Name	SUSTIVA®
Generic Name	Efavirenz
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Sponsor	Bristol Myers Squibb (BMS)
Formulation	Capsules
Indication	Treatment of HIV Infection
Population	HIV-1 Infected Pediatric Patients who are at least 3 months and weigh at least 3.5 kg
Review Team	Vikram Arya, Ph.D., Jeffry Florian, Ph.D., Islam Younis, Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY

Efavirenz (SUSTIVA®) is approved, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adult and pediatric patients. Efavirenz is available as capsules (200 mg and 50 mg) and as tablets (600 mg).The approved dose of efavirenz in adult patients is 600 mg taken orally once daily on an empty stomach, preferably at bedtime. The approved dosing of efavirenz in pediatrics is shown in Table 1.

Table 1. Approved Dosing of Efavirenz in Pediatrics

Pediatric Patients at Least 3 Years and at Least 10 kg (2.2)					
kg	lbs	dose	kg	lbs	dose
10 - <15	22 - <33	200 mg	25 - <32.5	55 - <71.5	350 mg
15 - <20	33 - <44	250 mg	32.5 - <40	71.5 - <88	400 mg
20 - <25	44 - <55	300 mg	at least 40	at least 88	600 mg

The sponsor is seeking approval of:

1. A new method of administering SUSTIVA® (sprinkling and mixing the contents of the approved capsule with various food vehicles) to adult and pediatric patients who cannot reliably swallow capsules or tablets.
2. New dosing recommendations for pediatric patients 3 months or older and weighing between (b) (4) kg and 10 kg. Of note, dosing recommendations of SUSTIVA® for pediatric patients weighing between 10 kg and 40 kg are part of the approved prescribing information of SUSTIVA®.

To support approval the applicant provided the results from the following trials:

1. **AI266059:** Bioavailability of Efavirenz Capsule Contents Mixed With Food Vehicles (Applesauce, Grape Jelly, or Yogurt) or Baby Formula Relative to the Intact Capsule Formulation Administered Under Fasted Conditions in Healthy Adult Subjects
2. **AI266922:** An open label study of liquid and sprinkled capsule formulations of efavirenz administered in combination with didanosine and emtricitabine in HIV-1 infected infants and children 3 months to 6 years of age.
3. **PACTG1021:** An open label study to evaluate the safety, tolerability, antiviral activity and pharmacokinetics of emtricitabine in combination with efavirenz and didanosine in a once daily regimen in HIV infected antiretroviral therapy naïve or very limited antiretroviral exposure in pediatric subjects.
4. **ACTG382:** Phase 1/2 open-label, AUC-controlled study to determine the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz in combination with nelfinavir in children.

The sponsor developed a population pharmacokinetic model based on data from the abovementioned trials. The model was used to construct EFV dosing in different weight groups based on matching simulated AUC with target adult AUC of 263 [233; 303] µM·h.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted in this NDA and the information provided supports the following conclusions:

- The Clinical Pharmacology information pertaining to similarity in systemic exposures of efavirenz after administration of efavirenz as an intact capsule or administration of efavirenz capsule contents mixed with different food vehicles is acceptable.
- The available pharmacokinetic and safety data collected in pediatric patients supports the following proposed dosing of efavirenz:

Table 2. Proposed dosing of Efavirenz in Pediatrics 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

New dosing recommendation is highlighted in **BOLD**.
* Dosing recommendations for the 10-15 kg are part of the currently approved Prescribing information; new dosing recommendations only apply to the 7.5-10 kg dose group.

The above recommendations are pending the results from the analytical and clinical site inspections which were not finalized at the time of this review.

1.2 Phase IV Commitments

None

1.3 Labeling Recommendations

The sections pertaining to dosage and administration and method of administration will be updated to reflect dosing of efavirenz in pediatric patients. Specifically, the following sections of the label will be revised:

- Highlights
  - Indication and Usage
  - Dosing and Administration
- Full Prescribing Information:
  - Section 1.2 (Pediatric Patients)
  - Section 1.3 (Capsule Sprinkle Method of Administration)
  - Section 6.2 (Clinical Trial Experience in Pediatric Patients)

- Section 8. 4 (Pediatric Use Section)
- Section 12.3 (Special Population)
- Section 14.2 (Pediatric Patients)
- Section 17.3 (Dosing Instructions)

In addition, references to CYP3A inhibitory properties of efavirenz will be deleted and information related to the CYP3A induction properties of efavirenz will be included in the pertinent section of the prescribing information. Please see the response to question 2.1.4 for additional information.

The final labeling language was under discussion at the time of finalizing this review.

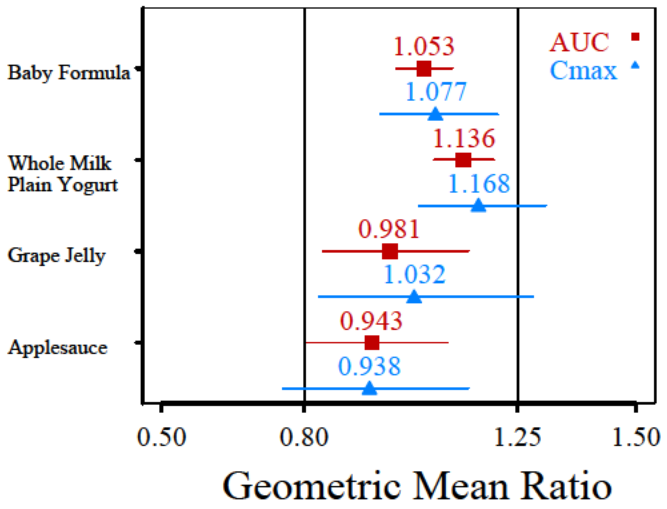
QUESTION BASED REVIEW SUMMARY

2.1 Specific Questions

2.1.1 Do the results of trial AI266059 support the administration of efavirenz capsule contents mixed with different food vehicles in the adult population?

Yes, the extent of EFV exposure (AUC) was similar after administration of efavirenz as an intact capsule or after administration of efavirenz capsule contents with different food vehicles: applesauce, grape jelly, yogurt, and baby formula (Figure 1). The lower bound of the 90 % CI for C_{max} of EFV was outside the 80-125 % limits when EFV capsule contents were mixed with apple sauce, grape jelly, and yogurt. This is not expected to be clinically relevant.

Figure 1. Statistical comparison (Treatment/Reference) of the pharmacokinetic parameters of EFV after oral administration of intact capsules (reference) and capsule contents mixed with food vehicles (Treatment).



2.1.2 Do the results from trials ACTG382, AI266922, and PACTG1021 support the proposed dosing recommendations in the pediatric patient population?

Yes, the sponsor's proposed dosing for pediatrics 3 months to ≤2 years of age is acceptable. This dosing includes extension of the 200 mg efavirenz dosing increment down to 7.5 kg, a dose of 150 mg efavirenz for pediatrics 5 to 7.5 kg, and a dose of 100 mg efavirenz for pediatrics (b) (4) to 5 kg. For the 100 mg dose, a decision was made to restrict the lower weight range to 3.5 kg based on the following items due to the following reasons:

1. Efavirenz mean predicted C_{max} and AUC in pediatrics <3.5 kg following the administration of 100 mg daily dose is predicted to be higher in pediatrics (b) (4) to 3.5 kg

because of the higher mg/kg that administered dose (40 to 28.6 mg/kg compared to 28.6 to 20 mg/kg).
2. Restrictions on dosing at lower weights which can only go in 50 mg increments.
3. The lowest body weight included in the trial (administered oral solution) was 3.3 kg and the lowest body weight pediatric administered sprinkles was 4.1 kg.
4. The 5th percentile body weight for a 3 month old pediatric subject (US CDC growth charts, female) is 4.5 kg. It was anticipated that providing dosing recommendations to a lower body weight than 3.5 kg may imply treatment is permissible in pediatrics <3 months of age.

The sponsor developed a population pharmacokinetic model based on data from the three trials in HIV-1 infected pediatrics (ACTG382, PACTG1021, and AI266922) and a fourth trial in healthy volunteers evaluating the bioavailability of 'sprinkled' efavirenz when administered with various vehicles compared to efavirenz administered as a capsule (fasted). 'Sprinkled' efavirenz refers to the sponsor's final age appropriate efavirenz formulation that involves opening efavirenz capsules and mixing the contents with an acceptable vehicle (grape jelly, applesauce, or yogurt) for administration to the subject. This pediatric formulation was ultimately selected due to lower than acceptable exposures from previous attempts at an age appropriate efavirenz formulation (i.e., solution which was used in a subset of subjects in PACTG1021 and AI266922). Pediatrics were only administered 'sprinkle' efavirenz in AI266922, though both ACTG382 and PACTG1021 contribute pediatric subjects administered efavirenz as either tablets or capsules. The final dataset included 168 pediatric subjects (3289 observations) and 24 adult subjects (1232 observations).

The applicant's final population pharmacokinetic model was used to obtain predictions of AUC_{ss}, C_{min}, and C_{max} for pediatrics <10 kg. While pediatric subjects were dosed at 400-600 mg initially if they had started on efavirenz oral solution or 300 mg efavirenz when initiating efavirenz treatment using 'sprinkles' in AI266922, the exposures observed in these pediatric subjects typically exceeded the upper range of the targeted adult exposure (380 µM·h). This was supported by the sponsor's modeling and simulation results which supports that pediatric doses of 200, 150, and 100 mg for pediatrics ≥7.5 to <10 kg, ≥5 to <7.5 kg, and ≥(b) (4) to 5 kg, respectively, are predicted to achieve pediatric exposures within the targeted adult AUC range specified in the label (190 to 380 µM·h, additional PK targets were evaluated but were considered secondary to AUC; C_{max}: 5.2 to 8.2 µg/mL; C_{min}: 1.9 to 2.9 µg/mL). Median (25th and 75th percentile) predictions from the sponsor's population pharmacokinetic model are shown below (Table 3). Initial steps evaluated by the sponsor use predicted efavirenz exposures for the <10 kg pediatric weight bands assuming all pediatrics would be administered 200 mg q.d (i.e., pediatrics (b) (4) to 10 kg administered 200 mg q.d.) Other scenario considerations included evaluating 150 mg q.d. for (b) (4) kg to 7.5 kg and 100 mg from (b) (4) kg to 5 kg. These results, summarized below, along with predictions for pediatrics >10 kg demonstrate that efavirenz 200 mg q.d. results in AUC exposures within the targeted interval for pediatrics 7.5 kg to 10 kg (predicted median [25th; 75th percentile] mean AUC from 1000 simulated trials: 284 [254; 321] µM·h). However, 200 mg was predicted to result in efavirenz AUC of 350 [309; 465] and 480 [405; 566] µM·h, respectively, exceed the specified upper limit of exposures. Due to the predicted higher exposure with this dosing, alternative regimens were explored in these pediatrics weight ranges and summarized in the same table. It was identified that efavirenz 150

mg q.d. was most appropriate in pediatric subjects 5 kg to 7.5 kg in order to achieve the targeted adult exposures (263 [233; 303] µM·h) while efavirenz 100 mg q.d. was most appropriate for pediatrics subjects (b) (4) kg to 5 kg (237 [202; 281] µM·h).

Table 3. Simulated Efavirenz Mean AUC Using Capsules/Sprinkles from 1000 Simulated Trials

Body Weight (Kg)	EFV Dose (mg)	AUC (25th; 75th)	[10th to 90th]
>= (b) (4) to <5	100	237 (202; 281)	[177; 331]
>= (b) (4) to <5	*150*	*359 (303; 424)*	*[267; 508]*
>= (b) (4) to <5	*200*	*480 (405; 566)*	*[356; 678]*
>=5 to <7.5	150	263 (233; 303)	[207; 347]
>=5 to <7.5	*200*	*350 (309; 465]*	*[277; 465]*
>=7.5 to <10	200	284 (254; 321)	[230; 364]
>=10 to <15	200	238 (216; 263)	[199; 289]
>=15 to <20	250	234 (215; 258)	[198; 285]
>=20 to <25	300	257 (238; 278)	[223; 309]
>=25 to <32.5	350	262 (241; 294)	[225; 325]
>-32.5 to <40	400	259 (242; 284)	[225; 314]
>=40	600	255 (228; 291)	[207; 323]

Table 4 displays predicted efavirenz C_{max} and C_{min} values for the proposed pediatric dosing. These predicted C_{max} and C_{min} values fall within the specified efaviranz values for these pharmacokinetic parameters (C_{max}: 5.2 to 8.2 µg/mL; C_{min}: 1.9 to 2.9 µg/mL) and further support the proposed efavirenz dosing.

Table 4. Simulated Efavirenz Mean AUC, C_{max}, and C_{min} Using Capsules/Sprinkles from 1000 Simulated Trials

Body Weight (Kg)	EFV Dose (mg)	AUC (25th; 75th)	Cmax (25th; 75th)	Cmin (25th; 75th)
>= (b) (4) to <5	100	237 (202; 281)	6.2 (5.3; 7.3)	2.6 (2.2; 3.2)
>=5 to <7.5	150	263 (233; 303)	7.1 (6.3; 8.1)	2.7 (2.3; 3.3)
>=7.5 to <10	200	284 (321; 254)	7.8 (7.0; 8.8)	2.9 (2.5; 3.4)
>=10 to <15	200	238 (216; 263)	6.5 (6.0; 7.2)	2.3 (2.1; 2.7)
>=15 to <20	250	234 (215; 258)	6.5 (6.0; 7.1)	2.3 (2.0; 2.6)
>=20 to <25	300	257 (238; 278)	7.0 (6.6; 7.6)	2.6 (2.3; 2.9)
>=25 to <32.5	350	262 (241; 294)	7.1 (6.5; 7.9)	2.7 (2.4; 3.1)
>-32.5 to <40	400	259 (242; 284)	7.0 (6.5; 7.7)	2.7 (2.4; 3.0)
>=40	600	255 (228; 291)	6.6 (6.0; 7.5)	2.8 (2.5; 3.3)

2.1.3 How does efavirenz exposure change in CYP2B6 poor metabolizers?

As observed previously (Dr. Liu and Dr. Pacanowski, Clinical Pharmacology Review, 12/12/2011) CYP2B6 genotype, specifically the 516 G>T substation on *6 haplotype had a considerable effect on efavirenz exposure. In the original review, subjects with 516 T/T genotype had a 2- to 3- folder increase in AUC, C_{max}, and C_0 compared to subjects with the G/G genotype. Subjects with the G/T genotype had a 1.3-fold higher AUC compared to subjects with G/G genotype. The current analysis from the sponsor updated based on 28 pediatrics subjects from AI266922 (14 subjects with G/G genotype, 13 subjects with G/T genotype, and 1 subject with T/T genotype) with CYP2B6 genotype data further supports these observations. A 1.4-fold increase in AUC was predicted for subjects with G/T genotype compared to G/G genotype while a 10-fold increase in AUC was predicted for subjects with T/T genotype compared to G/G genotype. It is likely that this higher estimate in subjects with T/T genotype is driven by the small sample size in the current study (one subject with T/T genotype), but the results from the updated analysis are otherwise qualitatively similar to those previously reported by the sponsor and to results published in the literature.

While higher exposures are observed in subjects with T/T genotype, no clear relationship between higher exposures and adverse events of interest were identified from the pediatric population. However, efavirenz was reported to induce QTc prolongation and torsades de pointes[1]. Time matched difference in (QTC)F interval at steady state of EFV compared to single dose administration showed that *CYP2B6*6* allele carriers (*1/*6 and *6/*6) may be at an increased risk for EFV-induced QTF interval prolongation at steady-state[2]. It is difficult to interpret the results of this analysis as no efavirenz exposure-response analysis was performed for this publication and no thorough QT study was ever performed with efavirenz. However, it was observed that C_{max} was approximately 2-fold higher in poor metabolizers compared to regular metabolizers in the previous Clinical Pharmacology Review (Dr. Liu and Dr. Pacanowski, Clinical Pharmacology Review, 12/12/2011). If an efavirenz concentration-QT relationship is later identified, subjects classified as poor metabolizers may be at increased risk of QT prolongation.

2.1.4 Should the prescribing information be updated to reflect the CYP3A induction properties of efavirenz?

Yes, the prescribing information should be updated to include information related to CYP3A induction potential of efavirenz. Information in the current approved prescribing information pertaining to the CYP inhibition potential of efavirenz is based on in vitro studies. Data collected from several drug-drug interaction trials suggest that efavirenz is a CYP3A inducer. For example, the clinical recommendation pertaining to immunosuppresants (Table 6 in Section 7.1 of the EFV label) indicates that "decreased exposures of the immunosuppressant may be expected due to CYP3A induction". Hence, prescribing information should be updated to reflect the CYP3A induction potential of efavirenz.

---

[1] Castillo R, Pedalino RP, El-Sherif N, Turitto G. Efavirenz-associated QT prolongation and Torsade de Pointes arrhythmia. Ann Pharmacother. 2002 Jun;36(6):1006-8.

[2] Abdelhady AM, Thong N, Kreutz Y, Tisdale JE, Desta Z, Overholser BR. Association of the CYP2B6*6 allele with efavirenz-induced QT interval changes at steady state in healthy volunteers. CPT. 2013 Feb;93:S22-S23

Individual Study Reviews

Study AI266059

Title

Bioavailability of Efavirenz Capsule Contents Mixed With Food Vehicles (Applesauce, Grape Jelly, or Yogurt) or Baby Formula Relative to the Intact Capsule Formulation Administered Under Fasted Conditions in Healthy Adult Subjects

Objectives

Primary Objective:

To assess the bioavailability of efavirenz capsule contents when mixed with one of three food vehicles (applesauce, grape jelly, or yogurt) or baby formula, relative to the intact capsule formulation administered under fasted conditions.

Study Design

Open-label, randomized, three-period, three-treatment cross over study design in twenty four healthy adult subjects (12 subjects/treatment group). Subjects underwent screening evaluations to determine eligibility within 21 days prior to study enrollment. For each period, subjects were admitted to the clinical facility in the evening prior to dosing (Days -1, 20, and 40). On Day -1, Period 1, subjects were randomly assigned to one of twelve treatment sequences (6 treatment sequences per treatment group). Treatment Group I received treatments A, B and C, while Group II received Treatments A, D and E.

- 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.

In 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).

Prior to administration, the contents of the capsule were gently mixed with the food vehicle in a 100 mL polypropylene container. After subjects consumed the dosing mixture from the polypropylene container (Treatments B-E), the container was rinsed three times with 50 mL of

water and the subject swallowed each rinse. A total of 240 mL of water was consumed at the time of study drug administration. The remaining 90 mL of water was administered to the subject after the three rinses were swallowed. The time of dose administration was assigned the "0" hour time-point. Subjects were instructed to maintain an upright (seated or standing) position and remained fasted for at least 4 hours following administration of study drug. The polypropylene container for each subject was labeled appropriately with the subject's information and individually sealed inside a plastic bag.

Subjects were confined to the clinical facility until at least 168 hours (8 days) after dose administration for each treatment period. On Days 21 and 41, subjects were crossed over to the next treatment as specified by their assigned treatment sequence.

Formulation

Efavirenz (Sustiva®) was obtained from commercial sources. Table shows the formulation and batch # of Sustiva used in the trial.

Table 1: Formulation and Batch # of Sustiva Used in the Trial

Drug	Strength	Formulation	Route	Batch Number	Expiration Date	Appearance
Efavirenz (Sustiva®)	200 mg	Capsule	Oral	ESL435A	31-Dec-2007	Gold color, reverse printed with "SUSTIVA" on the body and imprinted "200 mg" on the cap.

AI266059

Sample Collection, Bioanalysis, and Pharmacokinetic Assessments

Sample Collection

Serial blood samples (4 mL) were obtained prior to and over a 21 day period after dosing at the following approximate times during each of the three study periods: prior to dosing (0 hour), and at 1, 2, 3, 4, 5, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 336, and 480 hours following dose administration. The last sample in each period (480 hours post-dose) also served as the pre-dose sample for the subsequent period. Subjects were required to return to the clinical study unit at specified times for plasma sample collection at 240, 336, and 480 hours post-dose administration during each study period.

Bioanalysis

The calibration samples for efavirenz ranged from 2 ng/mL to 1600 ng/mL. The LLOQ was 2 ng/mL. The quality control samples were prepared at four concentration levels (6, 75, 900, and 1200 ng/mL).

The % CV of the QCs ranged from 2.1to 8.6 % and the % RE (relative error) ranged from 2 to 7.8 %.

Pharmacokinetic Assessments

The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$) were computed by non-compartmental analysis using Kinetica™ 4.2.

To assess the bioavailability of efavirenz 3x200 mg capsule contents mixed with food vehicle relative to the efavirenz 3x200 mg capsules fasted, analyses of variance were performed on log(C_{max}), log(AUC[INF]) and log(AUC[0-T]) for each treatment group.

The factors in the analyses were sequence, subject within sequence, period, and treatment. Since subjects are random effects nested within sequences, F-statistics for sequence effects were the ratios of the Type I mean squares for sequence and subjects within sequence. Point estimates and 90% confidence intervals for the differences between treatments (efavirenz 3x200 mg capsule contents mixed with food versus efavirenz 3x200 mg capsules fasted) on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

Geometric means and coefficients of variation were provided by treatment for C_{max}, $AUC_{(INF)}$ and $AUC_{(0-T)}$. Means and standard deviations were provided by treatment for T-HALF. Medians, minima, and maxima were provided by treatment for T_{max}.

Results

Subject Disposition

Out of the 24 subjects enrolled in the trial, 21 subjects completed the trial. 3 subjects discontinued the trial (2 discontinuations due to adverse events [AST/ALT elevations] and 1 subject was lost to follow up). 22 subjects were included in the pharmacokinetic and statistical analysis.

One subject [randomized to group 2] who was lost to follow up completed up to day 48 of treatment period 3 and was lost to follow up post day 74. The subject did not provide the pharmacokinetic samples at 240, 336, and 480 hours. The available data from this subject was included in the pharmacokinetic and statistical analysis.

Table 2 shows the demographic characteristics of subjects enrolled in the trial.

Table 2: Demographic characteristics of subjects enrolled in the trial

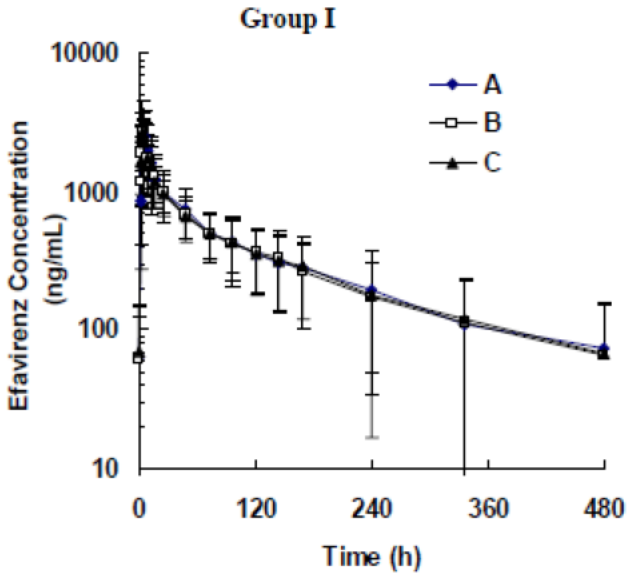
Characteristic	Treatment Group 1 (ABC)[a]	Treatment Group 2 (ADE)[a]	All Treated (n =24)
Age, years			
Mean	33	33	33
SD	7	7	7
Range	23-45	20-45	20-45
Gender, n (%)			
Male	11 (92)	12 (100)	23 (96)
Female	1 (8)	0 (0)	1 (4)
Race, n (%)			
White	8 (67)	4 (33)	12 (50)
Black/African American	4 (33)	8 (67)	12 (50)
Weight, kg			
Mean	77.8	83.4	80.6
SD	12.0	10.1	11.2
Range	59.6-90.3	61.6-98.1	59.6-98.1
Height, cm			
Mean	175.9	179.4	177.7
SD	7.3	4.6	6.2
Range	159.6-186.0	171.5-184.5	159.6-186.0
Body Mass Index (kg/m^2)			
Mean	25.1	25.9	25.5
SD	3.2	2.8	2.9
Range	20.0-29.2	20.3-29.0	20.0-29.2

AI266059
Source: Supplemental Tables S.8.3A and S8.3B
[a] A = 3x200 mg capsules fasted B = 3x200 mg + applesauce C = 3x200 mg + grape jelly, D = 3x200 mg + yogurt E = 3x200 mg + baby formula

Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time profile of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (applesauce [treatment B] and grape jelly [treatment C]).

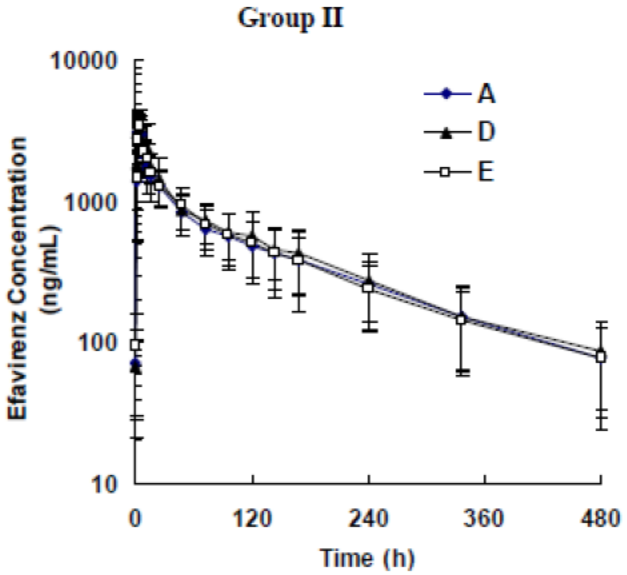
Fig 1: Mean plasma concentration-time profile of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (applesauce [treatment B] and grape jelly [treatment C])



Note: A = 3x200 mg capsules fasted
B = 3x200 mg + applesauce
C = 3x200 mg + grape jelly
AI266059
Source: Supplemental Table S.11.2.1A

Fig 2 shows the mean plasma concentration-time profile of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (yogurt [treatment D] and baby formula [treatment E]).

Fig 2: Mean plasma concentration-time profile of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (yogurt [treatment D] and baby formula [treatment E])



Note: A = 3x200 mg capsules fasted
D = 3x200 mg + yogurt
E = 3x200 mg + baby formula
AI266059
Source: Supplemental Table S.11.2.1A

Table 3 shows the mean pharmacokinetic parameters of efavirenz after administration of the various treatments.

Table 3: Mean pharmacokinetic parameters of efavirenz after administration of the various treatments

Group	Treatment [a]	Efavirenz Pharmacokinetic Parameters				
		Cmax (ng/mL) Geom. Mean (CV)	AUC(INF) (ng.h/mL) Geom. Mean (CV)	AUC(0-T) (ng.h/mL) Geom. Mean (CV)	Tmax (h) Median (min, max)	T-HALF (h) Mean (SD)
I (n = 10)	A	2693 (48%)	153067 (55%)	142788 (45%)	4.5 (2.0, 8.0)	117 (53)
	B	2475 (63%)	143269 (61%)	133213 (48%)	4.0 (2.0, 8.0)	125 (69)
	C	2772 (37%)	150170 (71%)	136038 (46%)	3.0 (1.0, 5.0)	149 (139)
II (n = 12)	A	3522 (29%)	192826 (39%)	179718 (36%)	3.0 (2.0, 4.0)	122 (40)
	D	4114 (27%)	219003 (32%)	204139 (29%)	4.0 (1.0, 12.0)	127 (41)
	E	3794 (23%)	202967 (33%)	189881 (30%)	4.0 (1.0, 12.0)	127 (39)

[a] A = 3x200 mg capsules fasted B = 3x200 mg + applesauce C = 3x200 mg + grape jelly,
D = 3x200 mg + yogurt E = 3x200 mg + baby formula
AI266059
Source: Supplemental Table S.11.2.1B

Table 4 shows the statistical comparison of the pharmacokinetic parameters of EFV after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (applesauce [treatment B] and grape jelly [treatment C]).

Table 4: Statistical comparison of the pharmacokinetic parameters of EFV after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (applesauce [treatment B] and grape jelly [treatment C])

Pharmacokinetic Variable	Geometric Means		Ratio of Geometric Means		
	Treatment [a]	Geometric Mean	Ratio	Point Estimate	90% Confidence Interval
Cmax (ng/mL)	A	2625	-	-	-
	B	2461	B vs A	0.938	(0.755, 1.164)
	C	2710	C vs A	1.032	(0.832, 1.282)
AUC(0-T) (ng.h/mL)	A	138770	-	-	-
	B	130289	B vs A	0.939	(0.836, 1.054)
	C	132680	C vs A	0.956	(0.852, 1.074)
AUC(INF) (ng.h/mL)	A	147408	-	-	-
	B	138930	B vs A	0.943	(0.807, 1.101)
	C	144630	C vs A	0.981	(0.840, 1.146)

[a] A = 3x200 mg capsules fasted B = 3x200 mg + applesauce C = 3x200 mg + grape jelly

AI266059

Source: Supplemental Tables S.11.2.1C, S.11.2.1D, and S.11.2.1E

Table 5 shows the statistical comparison of the mean pharmacokinetic parameters of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (yogurt [treatment D] and baby formula [treatment E]).

Table 5: Statistical comparison of the mean pharmacokinetic parameters of efavirenz after oral administration of intact capsules (treatment A) and capsule contents mixed with food vehicles (yogurt [treatment D] and baby formula [treatment E])

Pharmacokinetic Variable	Geometric Means		Ratio of Geometric Means		
	Treatment [aa]	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	3522			
	D	4114	D vs A	1.168	(1.042, 1.310)
	E	3794	E vs A	1.077	(0.961, 1.208)
AUC(0-T) (ng.h/mL)	A	179718			
	D	204139	D vs A	1.136	(1.070, 1.206)
	E	189881	E vs A	1.057	(0.995, 1.122)
AUC(INF) (ng.h/mL)	A	192826			
	D	219003	D vs A	1.136	(1.075, 1.200)
	E	202967	E vs A	1.053	(0.996, 1.112)

[a] A = 3x200 mg capsules fasted D = 3x200 mg + yogurt E = 3x200 mg + baby formula

AI266059

Source: Supplemental Tables S.11.2.1F, S.11.2.1G, and S.11.2.1H

Conclusion

- The extent of EFV exposure (AUC) was similar after administration of efavirenz as an intact capsule or after administration of efavirenz capsule contents with different food vehicles.
    - The lower bound of the 90 % CI for C_{max} of EFV was outside the 80-125 % limits when EFV capsule contents were mixed with apple sauce vs when EFV was administered as an intact capsule. This is not expected to be clinically relevant.
    - The upper bound of the 90 % C_{max} of EFV was outside the 80-125 % limits when EFV capsule contents were mixed with grape jelly vs when EFV was administered as an intact capsule. This is not expected to be clinically relevant.
    - The upper bound of the 90 % C_{max} of EFV was outside the 80-125 % limits when EFV capsule contents were mixed with yogurt vs when EFV was administered as an intact capsule. This is not expected to be clinically relevant

Study **AI266922**

Title

An Open-label Study of Liquid and Sprinkled Formulations of Efavirenz Administered in Combination with Didanosine and Emtricitabine in HIV-infected Infants and Children 3 Months to 6 Years of Age

Objectives

Primary Objective:
To characterize the pharmacokinetic (PK) properties of efavirenz (EFV) in oral solution formulation and capsule formulation given as a sprinkle preparation in infants and children 3 months to 6 years of age.

Study Design
This was a Phase 2 prospective, open-label, multicenter study of 48 weeks duration. Subjects < 3 years of age at Week 48 were to continue until their 3rd birthday. All subjects enrolled in countries where EFV oral solution was not commercially available could remain on study until their 7th birthday or until they were able to swallow EFV capsules (whichever occurred first). There were 4 age groups of HIV-infected infants and children. Accrual into these groups occurred concurrently.
• Group 1: 15 infants, ≥ 3 months to < 6 months of age
• Group 2: 10 infants, ≥ 6 months to < 2 years of age
• Group 3: 4 children, ≥ 2 to < 3 years of age
• Group 4: 8 children, ≥ 3 to ≤ 6 years of age (until their 7th birthday).

Number of subjects (Planned and Analyzed): Thirty-two subjects were planned for the analyses. Fifty-six subjects were enrolled, and 37 subjects were treated.

Criteria for evaluation:
Efficacy:
• Proportion of subjects with HIV RNA < 50 and < 400 c/mL at Week 48
• Log10 c/mL HIV RNA changes from baseline through Week 48
• CD4 cell count and CD4 percent changes from baseline through Week 48.

Safety: Safety variables included the frequency of adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), discontinuation from study therapy due to AEs, acquired immunodeficiency syndrome, laboratory abnormalities, and physical examination and vital signs findings.

Pharmacokinetic Assessments
PK parameters of EFV and ddI were derived from plasma concentration versus time data at Weeks 2, 10, and 18. Blood samples for determination of plasma EFV and ddI were collected before study drug administration and at 0.5, 1, 3, 5, 8, and 24 hours after study drug

administration from an indwelling catheter or by direct venipuncture. The PK parameters assessed were C_{max}, C_{min}, AUC, CL/F, CL/F/kg, and half-life.

Results:

Disposition and Baseline/Demographic Characteristics: Fifty-six subjects were enrolled, but 19 subjects (34%) were never treated. The most common reasons for not being treated were that the subject no longer met study criteria (9 subjects [16%]) and "other" reasons (6 subjects [11%]). Thirty-seven subjects were treated. Ten subjects (27%) discontinued study therapy prior to Week 48 and 9 subjects (24%) discontinued study therapy at or after Week 48. The most common reason for discontinuation of study therapy was lack of efficacy. At baseline, the majority of treated subjects were White and male, with a median age of 0.7 years

Efficacy results:

By Week 48, the proportion of subjects who achieved HIV RNA < 50 c/mL and < 400 c/mL, using the CVR analysis, was 49% and 57%, respectively. Using the VR-OC analysis, the proportions of subjects who achieved HIV RNA < 50 c/mL and < 400 c/mL were 63% and 78%, respectively. Using the snapshot algorithm analysis, the proportions of subjects who achieved HIV RNA < 50 c/mL and < 400 c/mL were 46% and 57%, respectively. These results varied by age group.

By Week 48, subjects in all age groups achieved median changes in log10 HIV RNA from baseline that ranged from -2.92 to -3.27 c/mL, with a median of -3.18 c/mL. At Week 48, subjects had higher median CD4 cell counts and CD4 percents compared with baseline, except in Group 1, where the median change from baseline in CD4 counts was -258 cells/mm3versus 346, 971, and 284 cells/mm3 in Groups 2, 3, and 4, respectively

Safety results:

There were no new or unexpected safety events reported, and in most cases, AEs were not treatment limiting. Four deaths were reported (2 before receiving treatment). Deaths in the 2 treated subjects were not considered drug related by the investigators. Fifty-four percent of subjects had SAEs, and 2 subjects discontinued study therapy due to AEs. The majority of subjects had AEs, typically Grade 1 or 2, and the most common AEs were diarrhea, nasopharyngitis, pneumonia, and pharyngitis. The incidence of the AEs of special interest, nervous system symptoms, hepatic toxicity, and rash-related events, was low.

Pharmacokinetic results:

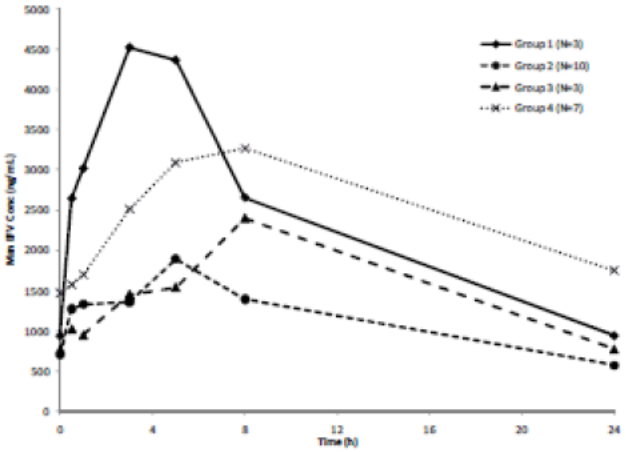
EFV PK parameters at Week 2 are summarized by age group and formulation below. EFV exposures were highly variable in pediatric subjects ≥ 3 months to ≤ 6 years of age. After administration of the oral solution at body weight-based doses projected to provide exposures comparable to adults, EFV AUCs were often suboptimal (< 110 μM•h), while the capsule sprinkle tended to produce EFV AUC within the target range (110 to 380 μM•h). EFV clearance adjusted by body weight appears to be inversely correlated with age in pediatric subjects ≥ 3 months to ≤ 6 years of age

Table 1: Summary of EFV Pharmacokinetic Parameters at Week 2 (by Age and Formulation)

Group	Formulation	N	Cmax (ng/mL) Geo. Mean (%CV)	AUC(TAU) (µM•h) Geo. Mean (%CV)	Cmin (ng/mL) Geo. Mean (%CV)	CLT/F (L/h) Geo. Mean (%CV)	CLT/F/kg (L/h/kg) Geo. Mean (%CV)
1	Oral Solution	3	3790 (76)	130 (98)	391 (141)	9.54 (63)	2.07 (71)
	Capsule Sprinkle	9	10543 (45)	353 (68)	2229 (103)	2.78 (81)	0.431 (73)
2	Oral Solution	10	1998 (51)	71.4 (49)	445 (57)	19.7 (85)	2.36 (84)
3	Oral Solution	3	2167 (68)	93.8 (68)	648 (75)	13.1 (58)	1.44 (51)
	Capsule Sprinkle	1	14400 (N/A)	742 (N/A)	5650 (N/A)	2.56 (N/A)	0.196 (N/A)
4	Oral Solution	7	2632 (83)	131 (98)	1185 (111)	9.11 (73)	0.656 (72)

Mean EFV plasma concentrations versus time profiles for each group at Week 2 for the oral solution are shown in Figure 2.

Figure 2: Mean Plasma Concentration-time Profiles for Efavirenz by Age Group in Pediatric Subjects Treated with the Oral Solution at Week 2 (Upper: Linear Scale; Lower: Log-linear Scale)

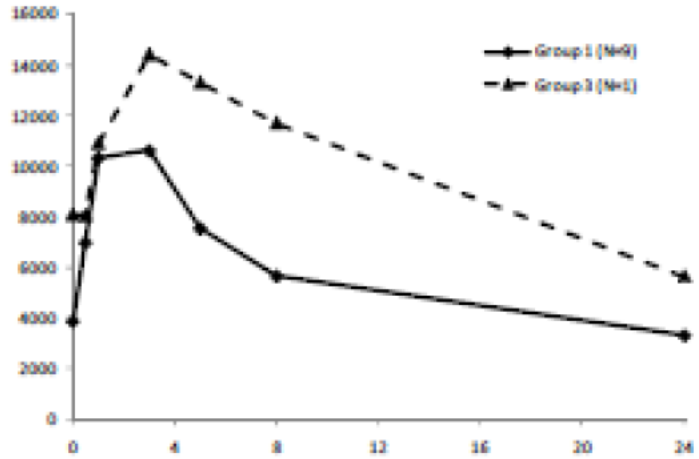


Sponsor's csr-interim-week-48.pdf, pg 114

Sixteen subjects in Groups 1, 2, and 3 initiated the study on EFV oral solution. Of those subjects, 11 required a switch to the capsule sprinkle formulation at Week 8 due to suboptimal EFV AUC(TAU) (< 110 µM•h) and returned to the clinic at Week 10 for repeat intensive PK sample collections. Of those 11 subjects, 10 had evaluable EFV PK at Week 10.

Of the 10 subjects with evaluable PK at Week 10, 6 required a decrease in EFV capsule sprinkle dose at Week 16 and returned for a third intensive PK sample collection visit at Week 18. All 6 of these subjects were in the youngest age groups: Group 2 (N=5) or Group 1 (N=1). Subjects enrolling in the study after implementation of Amendment 3 initiated the study on the capsule sprinkle, and the dosing nomogram used to estimate starting doses was modified so that a relatively reduced dose of capsule sprinkle was used. The revised capsule sprinkle dosing nomogram for subjects < 2 years of age was 1,200 mg x (body weight/70)$^{0.7}$. Mean EFV plasma concentration versus time profiles for each group at Week 2 for the capsule sprinkle are shown in Figure 3.

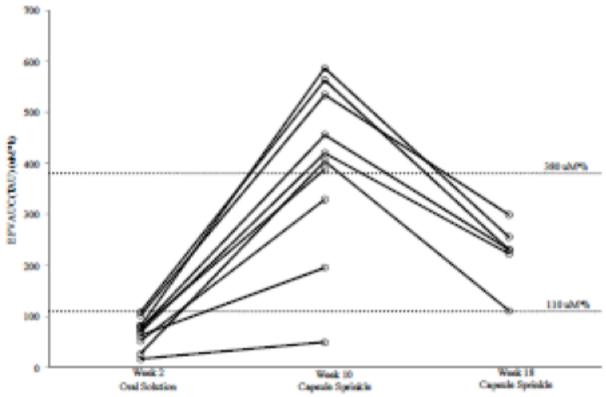
Figure 3: Mean Plasma Concentration-time Profiles for Efavirenz by Age Group in Pediatric Subjects Treated with the Capsule Sprinkle at Week 2 (Upper: Linear Scale; Lower: Log-linear Scale)



Sponsor's csr-interim-week-48.pdf, pg 117

As described above, the oral solution generally provided suboptimal EFV AUC(TAU) (i.e., < 110 µM•h) in subjects < 3 years of age. Those subjects with suboptimal EFV AUC(TAU) at Week 2 after treatment with the oral solution were switched to the capsule sprinkle formulation at Week 8 with a repeat intensive PK visit at Week 10. Many of those subjects subsequently had EFV AUC(TAU) values above the upper threshold of the target range (> 380 µM•h). Capsule sprinkle doses were reduced at Week 16 with a third intensive PK visit at Week 18. By Week 18, all subjects still on study that had suboptimal exposures at Week 2 with the oral solution were receiving a capsule sprinkle dose that provided an EFV AUC(TAU) within the target range (Figure 4).

Figure 4: Scatter Plot of Efavirenz AUC(TAU) for Subjects < 3 Years of Age That Initiated Treatment with the Oral Solution and Required a Switch to the Capsule Sprinkle



Sponsor's csr-interim-week-48.pdf, pg 121

Conclusion

- EFV oral solution administered at doses projected to provide exposures similar to those observed in adults produced suboptimal exposures (AUC < 110 µM•h) in pediatric subjects < 3 years of age. On the other hand, administration of the contents of the opened EFV capsule in a small amount of food (capsule sprinkle) at doses projected to provide

exposures similar to those observed in adults provided AUC values within the target range of 110 to 380 μM•h in pediatric subjects < 3 years of age.

- EFV oral clearance adjusted by body weight appears to be inversely related to age in pediatric subjects ≥ 3 months to ≤ 6 years of age treated with EFV oral solution.

Study **PACTG 1021**

Title

An Open-label Study to Evaluate the Safety, Tolerance, Antiviral-Activity and Pharmacokinetics of Emtricitabine in Combination with Efavirenz and Didanosine in a Once Daily Regimen in HIV Infected Antiretroviral Therapy Naïve or Very Limited Antiretroviral Exposed Pediatric Subjects

Objectives

Primary Objective:
• To determine the long-term safety and tolerance of a regimen of FTC + EFV + ddI administered once daily (QD) in HIV-infected pediatric subjects who are naïve, or have very limited exposure, to antiretroviral (ARV) therapy.
• To determine the antiviral activity of a regimen of FTC + EFV + ddI administered once daily in treatment of naïve, or very limited ARV-exposed, pediatric subjects.
Secondary Objective:
• To determine EFV systemic exposure following administration of the currently recommended pediatric doses.
• To evaluate, in exploratory fashion, whether administration of the contents of an EFV capsule dispersed in a food vehicle (capsule sprinkles) represents a viable dosing strategy.

Study Design
The PACTG was responsible for implementation of the protocol and preparation of the database. Study PACTG 1021 was a Phase 1/2 open label study evaluating the safety, tolerance, antiviral activity and PK of FTC in combination with EFV and ddI in a QD regimen in HIV-infected pediatric subjects aged 90 days to < 22 years. All study subjects were either absolutely naïve to ARV therapy, had received ≤ 56 days perinatal prophylaxis or < 7 days of cumulative ARV therapy prior to study entry, and had screening plasma HIV-1 RNA levels ≥ 5000 copies/mL (c/mL).Subjects were enrolled based on their age at entry. The study consisted of 3 age groups:

Group 1 – 90 days to < 3 years of age
Group 2 - 3 years to < 13 years of age
Group 3 - 13 to < 22 years of age.

Number of subjects:
A total of 43 subjects were treated with EFV in Groups 1, 2, and 3 in PACTG 1021. Six subjects were enrolled and treated in Group 1, 21 subjects were enrolled and treated in Group 2, and 16 subjects were enrolled and treated in Group 3.

Test product, dose, mode of administration, duration of treatment, and batch number:
Subjects were administered a regimen of emtricitabine (FTC) + EFV + didanosine (ddI) QD. Efavirenz was available as a 30-mg/mL oral solution and 50-, 100-, or 200-mg strength capsules. Efavirenz was administered QD in the evening (Groups 2 and 3) or in the morning (Group 1 for 12 weeks) with FTC and ddI. Group 1 subjects weighing < 10 kg were given 390 mg QD EFV

and subjects weighing 10 kg to 32.5 kg were given 600 mg QD EFV. For subjects in Group 1 who had an AUC below the threshold value, EFV capsule sprinkles were administered. Group 2 and Group 3 subjects were given up to a maximum of 600 mg QD capsules or 720 mg oral solution EFV. Subjects in Group 1 were dosed for 96 weeks and subjects in Groups 2 and 3 were dosed for 192 weeks.

Lot numbers for the 50-mg EFV capsule were ERF413A, ESF227B, ESO509B, RH523A, SF585A, TP141D, and UE380D. Lot numbers for the 100-mg EFV capsule were ERF415A, ESA051A, ESL438B, RN941A, SN080D, TF551A, and UC159A. Lot numbers for the 200-mg EFV were 7F30603B, 7L32764A, EPJ340A, EQD144A, EQF235A, ERH430A, ERJ490A, ERK536B, ESA060A, ETD197A, PN808A, and RJ693A. Lot numbers for the 30mg-mL oral solution were 013371A, 013371C, 013435A, 2D63298, 2G61509, 2G62465, 3A65986, 3G74059, 5A10862, 5H08592, and 6D15658

Criteria for evaluation:
Efficacy:
• Proportion of subjects with HIV RNA < 50 and < 400 c/mL at Week 48
• Log10 c/mL HIV RNA changes from baseline through Week 48
• CD4 cell count and CD4 percent changes from baseline through Week 48.

Safety: The following safety endpoint was assessed for this report:
- The frequency of AEs and serious adverse events (SAEs).
- The frequency of deaths.
- The frequency of laboratory abnormalities.

Pharmacokinetic Assessments
Pharmacokinetic parameters of EFV were derived from plasma concentration versus time data. Some of the parameters included: maximum observed plasma concentration (Cmax), trough plasma concentration (Cmin), and area under the plasma concentration-time curve from time 0 to 24 hours post dose administration in 1 dosing interval (AUC[TAU]).

Results:
Disposition and Baseline/Demographic Characteristics:
A total of 43 subjects (6 in Group 1, 21 in Group 2, and 16 in Group 3) were enrolled and treated with EFV. A majority of subjects (58.1%) completed 48 weeks of treatment. The most common reasons for discontinuation were that the subject reached a protocol-defined clinical event, disease progression or laboratory endpoint (8 subjects), or the subject was no longer able to attend clinic (4 subjects).

The median baseline HIV RNA level for all subjects was 4.8 log10 c/mL and was comparable between age groups. Subjects in Group 1, Group 2, and Group 3 had median baseline CD4 cell counts of 1532 cells/mm3, 374 cells/mm3, and 276 cells/mm3, respectively. The median time on study therapy for subjects in Group 1, Group 2, and Group 3 was 95.1, 205.1, 164.2 weeks, respectively.

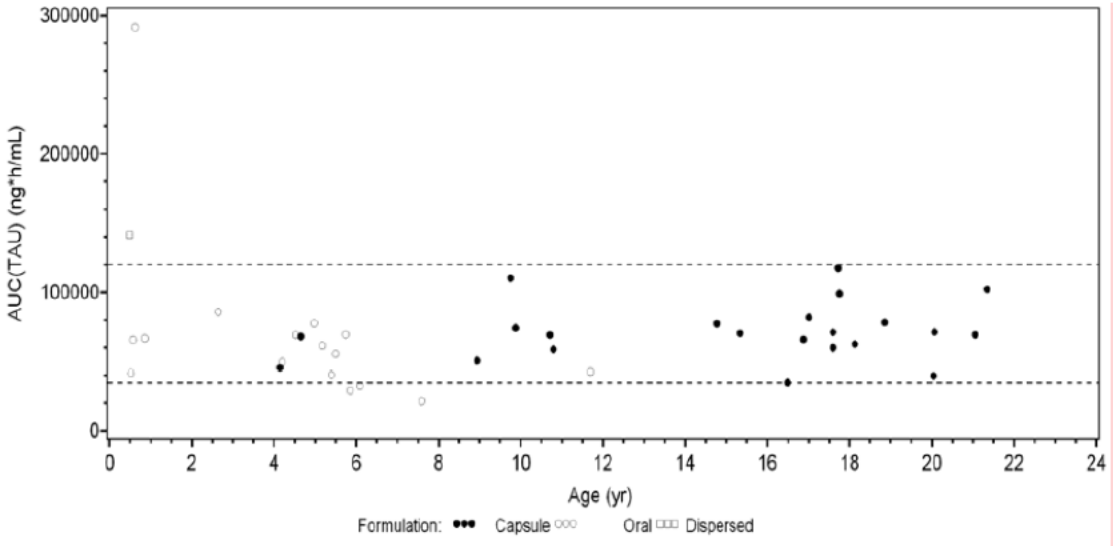
Efficacy Results:

In all groups, the proportion of subjects with HIV RNA < 400 copies/mL (VR-OC) at 48 weeks was 94.4% and varied by age group (75% in Group 1, 94.7% in Group 2, and 100% in Group 3); this response was maintained through Week 96 (all groups) and Week 192 (Groups 2 and 3) for subjects who remained on study. Generally, Group 1 subjects had an overall lower response rate than subjects in Groups 2 and 3. Overall, subjects in Groups 2 and 3 had higher median CD4 cell counts and CD4 percents compared with baseline; this response was maintained through Week 192 for subjects who stayed on study.

Safety Results:
There were no new or unexpected safety events reported in this study that were not reported in prior adult and pediatric studies with EFV; AEs were not treatment limiting in most cases. The safety data represent all available safety information from the start of the study until last-patient-last-visit (13-Jan-2009).

Pharmacokinetic Results:
The EFV dose was individually adjusted in subjects if their EFV AUC(TAU) fell outside the protocol defined target range of 110 to 380 μM*h (34725 to 119958 ng*h/mL). This range represents the estimated 10th and 90th percentiles of EFV AUCs observed in older pediatric subjects and adults. For subjects whose EFV AUC(TAU) fell outside the target exposure range, a dose adjustment was made at a subsequent visit and an additional intensive PK sample collection was conducted approximately 2 weeks later. This was repeated until a dose that achieved an EFV AUC(TAU) within the target exposure range was identified. A scatter plot of EFV AUC(TAU) versus age by formulation after the final dosing regimen (identified as the dose with intensive PK sample collection on or before Week 16) is displayed in Figure 5. Summary statistics for EFV dose and selected PK parameters for the final dosing regimen are provided in Table 4.

Figure 5: Scatter plot of EFV AUC(TAU) versus Age by Formulation After the Final Dosing Regimen and Intensive PK Visit on or Before Week 16



Reference lines at 34725 ng*h/mL (110 μM*h) and 119958 (380 μM*h) correspond to the target EFV AUC range.

Note: "Oral" refers to the EFV oral solution; "Dispersed" refers to EFV capsule contents dispersed in food.

Sponsor's csr-final.pdf, pg 11

Table 4: Summary Statistics for Efavirenz Dose and Selected Pharmacokinetic Parameters for the Final Dosing Regimen

Age Group and Formulation	N	Mean Dose (mg)	Mean Dose (mg/kg)	Cmax (ng /mL) Geo. Mean (%CV)	AUC(TAU) (ng*h/mL) Geo. Mean (%CV)	Cmin (ng /mL) Geo. Mean (%CV)
1 Oral Solution	5	393	45.2	5151 (71)	85545 (93)	2093 (107)
1 Capsule Dispersed[a]	1	400	69.9	9605	141499	1709
2 Capsule	7	350	13.4	5158 (28)	68529[b] (31)	1893 (35)
2 Oral Solution	13	351	17.9	3240 (34)	48798[c] (33)	1294 (37)
3 Capsule	15	600	8.7	4700 (31)	70141 (30)	2036 (46)

[a] %CV not calculated for N = 1; [b] N = 6; [c] N = 11.

Note: final dosing regimen defined as the dose and formulation with intensive PK evaluation on or before Week 16.

Sponsor's csr-final.pdf, pg 12

CONCLUSIONS:

- Virologic suppression was observed with EFV + FTC + ddI in all age groups by Week 48 (as measured by HIV RNA) and persisted through Weeks 96 and 192 for subjects who remained on study.
- Efavirenz, administered with FTC and ddI, was generally safe and well tolerated across all age groups who were naive or had very limited exposure to ARV therapy, regardless of formulation. No new safety findings were identified in the pediatric population compared to adults.
- The current dosing recommendations for EFV capsule and oral solution provide EFV exposures (AUC) in HIV-infected patients between 3 and 21 years of age similar to the exposure range observed in adult patients receiving EFV 600 mg QD.
- Data from this study alone are insufficient to define dosing recommendations for either the EFV oral solution or capsule sprinkle in HIV-infected patients younger than 3 years of age.

Study **PACTG 382**

Title

A Phase 1/2, Open-Label AUC-Controlled Study to Determine the Pharmacokinetics, Safety, Tolerability, and Antiviral Activity of DMP 266 (Efavirenz) in Combination with Nelfinavir in Children.

Objectives

Primary Objective:

- The primary objective for Cohort I was to determine the dosing regimen of EFV in combination with NFV and to study the safety profile of EFV in combination with NFV.
- The primary objective for Cohort II was to define the PK and safety of a liquid preparation of EFV in combination with NFV in HIV-infected infants and young children.

Study Design

The study population included subjects who were naive to non-nucleoside reverse transcriptase inhibitor (NNRTI)- and protease inhibitor (PI)-therapy with plasma HIV RNA > 400 c/mL at entry. Initially, subjects in Cohort I were required to be on 1 or more nucleoside reverse transcriptase inhibitors (NRTIs) prior to entry into the study and had the option of concomitant use of NRTIs. However, Version 2.0 of the protocol required concomitant use of NRTIs for all subjects. NRTIs were not provided through the protocol. During the study, subjects in Cohort I must have received concomitant therapy with 1 or more NRTIs and ARV-naive subjects in Cohort II must have initiated therapy with 2 NRTIs in addition to study drug. If currently receiving NRTIs, subjects must have continued them throughout the study. Version 2.0 also added the evaluation of an EFV 20 mg/mL (sugar-containing) oral solution in combination with NFV in Cohort II for children who were 3 months to 8 years of age. Version 4.0 of the protocol allowed for 208 weeks of follow-up. EFV dosing was based on weight, tolerability, and AUC.

The study consisted of 2 cohorts:

- Cohort I: subjects 3 to 16 years of age treated with EFV capsules
- Cohort II: subjects treated with EFV oral solution, divided into the following 2 age strata: Stratum 1 (age $\geq$ 3 months and $<$ 2 years) and Stratum 2 (age $\geq$ 2 years and $\leq$ 8 years).

Number of Subjects:

A total of 102 subjects were treated with EFV in Cohorts I and II in PACTG 382. In Cohort I, 57 subjects were enrolled and treated. In Cohort II-Strata 1 and 2, 26 and 19 subjects, respectively, were enrolled and treated.

Test product, dose, mode of administration, duration of treatment, and batch numbers:

EFV was available in 3 formulations: hard capsules, 20-mg/mL oral solution and 30-mg/mL sugar-free oral solution; capsules were supplied as 50-, 75-, 100- or 200-mg strengths. Efavirenz was administered once daily in the morning either on an empty stomach or with food for 208 weeks. Lot numbers for 50-mg capsule were 003206A, 971983A, 971983B, RH523A, SF585A, TP141D, UE380D; 75-mg capsule were 971982A, 971982B; 100-mg capsule were ERF415A,

ESL438B, P0912B, RN941A, RN941A, SN080D, TF551A, 971976H, 971997B, 972002A, 972002B, 972003D, 972004A, 972005D, 972005F, 972006B; and 200-mg capsule were 983037B, 983041D, 993114B, 993114H, 993114M, 993114U, 993185B, 993185C, 993185G, EPJ340A, EQC135A, RJ693A, RJ693A; 20-mg/mL oral solution: 983007C, 983007D, 983011B, 983011C, 983011D, 983011E; and 30mg-mL sugar-free oral solution: 013371A, 013371A, 013371C, 013435A, 2D63298, 2G61509, 2K66118, 3A65986, 3G74059, 5A10862, 5A10862, 5A10862, 5H08592, 6D15658, 993142B.

CRITERIA FOR EVALUATION:

Efficacy Endpoints:

- Proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL.
- Log10 c/mL HIV RNA change from baseline.
- CD4 cell count and CD4 percent change from baseline.

Safety Endpoints:

The frequency of AEs, serious adverse events (SAEs), and laboratory abnormalities.

Pharmacokinetic Endpoints:

Pharmacokinetic parameters of EFV are derived from plasma concentration versus time data. The parameters to be assessed include: maximum concentration of drug (Cmax), minimum concentration of drug (Cmin), area under the curve. For Cohort I subjects, 24-hour PK sampling (obtained at predose, 2, 5, 6, 8, 12, and 24 hours post-dose) was performed at Weeks 2, 6, (and Week 10 as needed), 56, and 112. At Weeks 4 and 8 (and 12, etc, as needed), the EFV dose was adjusted if needed. For Cohort II subjects, 12-hour PK sampling (obtained at predose, 2, 5, 8, and 12 hours post-dose) was performed at Weeks 2 (and 6, etc, as needed), 56, and 112. At Weeks 4 (and 8, etc as needed), the EFV dose was adjusted if needed.

Results:

Disposition and Baseline/Demographic Characteristics

A total of 102 subjects were treated with EFV in PACTG 382, 57 in Cohort I and 26 in Cohort II-Stratum 1, and 19 in Cohort II-Stratum 2. Twenty-five subjects (13 in Cohort I and 12 in Cohort II) discontinued prior to Week 48, 23 subjects (13 in Cohort I and 10 in Cohort II) discontinued at or after Week 48, and 54 subjects (31 in Cohort I and 23 in Cohort II) completed participation in the study (Table 1). The most common reasons for discontinuation were at the request of the patient, parent, legal guardian (11.8%); clinical endpoints as defined by the protocol (11.8%); and at the request of the investigator or sponsor (10.8%).

The median time on study therapy for all subjects was 118 weeks (range: 0.1 to 225.6 weeks). The median baseline HIV RNA level for all subjects was 4.57 log10 c/mL and was comparable between cohorts. Most of the subjects in Cohort I had baseline HIV RNA < 30,000 whereas subjects in Cohort II had variable baseline RNA. Subjects in Cohort I, Cohort II- Strata 1 and 2 and had median baseline CD4 cell counts of 686 cells/mm3, 1567 cells/mm3, and 639 cells/mm3, respectively, with a median CD4 cell count of 755 cells/mm3 for all subjects. The use of ARVs prior to the start of the study was common overall (87.3% of subjects). The use of ARV therapy (with the exception of NNRTIs) prior to the study was within the protocol inclusion/exclusion criteria for all subjects.

Efficacy Results:
The efficacy data focuses on results through Week 48 in ACTG 382. By Week 48, the proportion of subjects who achieved HIV RNA < 400 c/mL and < 50 c/mL, using the Virologic Response – Observed Cases (VR-OC) analysis, was 74% and 57.1%, respectively. Using the Confirmed Virologic Response (CVR) Non-Completer = Failure (NC = F) analysis, the proportion of subjects who achieved HIV RNA < 400 c/mL and < 50 c/mL was 58.8% and 43.1%, respectively.

Safety Results:
The safety data represent all available safety information from the start of the study (04-Nov-1997) until last-patient-last-visit (08-Jan-2007). The median time on study therapy for all subjects was 118 weeks (range: 0.1 to 225.6 weeks).

There were no new or unexpected safety events that were not reported previously. Adverse events were not treatment limiting in most cases. One death was reported in a treated subject more than 1 year after stopping study therapy. Six subjects discontinued due to study drug toxicity and SAEs were reported in 28 of 102 enrolled subjects (27.5%). The most frequently reported SAE (in > 5% of subjects) was maculopapular rash (8 of 102 subjects; 7.8%) and neutropenia (6 of 102 subjects; 5.9%). The incidence of nervous system symptoms and rash were 11.8% and 36.3%, respectively. Overall, Grade 3 to Grade 4 hematologic, liver function, and serum chemistry abnormalities were low with the exception of abnormal neutrophils that were experienced by 32.7% of all subjects. The most common Grade 3 to Grade 4 liver function abnormality was abnormal ALT experienced by 5 of 102 subjects (5%).

Pharmacokinetic Results:
Subjects in Cohort I (3 to 16 years of age) were treated with the EFV capsule with a starting dose derived using the allometric formula (EFV dose = (weight in kg/70)$^{0.7}$ X 600 mg).

Forty-nine (49) subjects in Cohort I treated with the EFV capsule formulation had evaluable EFV PK at Week 2. Of those 49 subjects, 22 (45%) had an EFV AUC within the target range (190 to 380 µM•h). Four (4) subjects (8%) had an EFV AUC > 380 µM•h while 23 subjects (47%) had an EFV AUC < 190 µM•h and required a dose increase at Week 4. At Week 2, the mean Cmax, Cmin, and AUC(TAU) for EFV were 4.46 µg/mL, 1.9 µg/mL, and 242 µM•h, respectively. Forty-six (46) subjects had evaluable PK at Week 6 and of those 46 subjects, 27 (59%) had an EFV AUC within the target AUC range. Six (6) subjects (13%) had an EFV AUC > 380 µM•h and 13 subjects (28%) had an EFV AUC < 190 µM•h. The mean Cmax, Cmin, and AUC(TAU) at Week 6 were 5.5 µg/mL, 2.0 µg/mL, and 256 µM•h, respectively. EFV exposures were similar between adult and pediatric subjects treated with the EFV capsule (adult data obtained from studies AI266003 , AI266004 and AI266021) (Table 5).

Table 5: Efavirenz Pharmacokinetic Parameters in HIV-Infected Adults and Pediatric Subjects after 2 Weeks of Treatment with the Efavirenz Capsule

PK Parameter		HIV-Infected Adults (N = 35)	HIV-Infected Children (Cohort I) (N = 49)
Cmax (µM)	Mean (SD)	12.9 (3.7)	14.1 (5.6)
Cmin (µM)	Mean (SD)	5.6 (3.2)	6.10 (4.7)
AUC(TAU) (µM•h)	Mean (SD)	184 (73)	242 (186)

Note: Cmax and Cmin for Cohort I were converted to µM for consistent presentation with historical data

Sponsor's csr-final.pdf, pg 9

The original starting dose for subjects < 2 years of age (Cohort II-Stratum 1) was: dose = (subject weight in kg/70 kg)0.7 x 720 mg.

This dosing alogrithm was similar to that of older children treated with EFV capsule in Cohort I, with the dose of EFV (720 mg) adjusted to account for the 20% lower bioavailability of the oral solution relative to the capsule. Twenty-one (21) subjects in Cohort II-Stratum 1 (≥ 3months to < 2 years of age) treated with the EFV oral solution had evaluable PK at Week 2. Of those 21 subjects, 16 (76%) had an EFV AUC < 190 µM•h while only 1 subject (5%) had an EFV AUC within the target range. Four (4) of 21 subjects (19%) had an EFV AUC > 380 µM•h. The mean EFV Cmax, Cmin, and AUC(TAU) for the subjects in Cohort II Stratum 1 at Week 2 were 3.8 µg/mL, 1.5 µg/mL and 191 µM•h, respectively. At the time version 5 of the PACTG 382 protocol was revised, the observed Week 2 AUCs for EFV for this age group (Cohort II-Stratum 1) were considerably lower than anticipated at 115 µM•h. It was assumed based on linear kinetics that a 65% increase in starting dose would yield an EFV AUC of 190 µM•h and, therefore, the revised allometric equation for determining the starting dose for subjects in Cohort II-Stratum 1 became: dose = (subject weight in kg/70 kg)0.7 x 1200 mg. The algorithm for determining the initial dose of EFV was subsequently revised for subjects enrolling under version 5 of the protocol. Therefore, the summaries include subjects treated with initial doses derived from 2 different algorithms. Twelve (12) subjects in Cohort II-Stratum 1 had evaluable Week 2 EFV PK after the dosing algorithm was revised. The median (range) EFV AUC in these subjects was 139 µM•h (22 to 432 µM•h), a value that is still below the minimum target AUC of 190 µM•h defined in the protocol (Table 6). The original algorithm using a base EFV dose of 720 mg produced adequate EFV exposures in children 3 years of age and older (Cohort II-Stratum 2), but did not produce adequate EFV exposures in pediatric subjects younger than 2 years of age.

Table 2: Summary Statistics for EFV Pharmacokinetic Parameters for Subjects in Cohort II-Stratum I that Received the Oral Solution at a Dose Based on Algorithm 1 and Algorithm 2

Algorithm [N]	Cmax (µg/mL)	AUC(TAU) (µM•h)	Cmin (µg/mL)
1 [9]			
Geo. Mean (%CV)	3.39 (77)	156 (104)	0.906 (151)
Median (min, max)	2.63 (1.58 - 11.3)	117 (55 - 755)	0.831 (0.12 - 9.46)
2 [12]			
Geo. Mean (%CV)	2.71 (83)	132 (75)	0.902 (81)
Median (min, max)	2.86 (0.58 - 9.90)	139 (22 - 432)	1.10 (0.00 - 3.09)

Algorithm 1: EFV dose = (subject weight in kg/70 kg)$^{0.7}$ x 720 mg

Algorithm 2: EFV dose = (subject weight in kg/70 kg)$^{0.7}$ x 1200 mg

Sponsor's csr-final.pdf, pg 10

Stratum 2: Subjects in Cohort II-Stratum II (≥ 2 years to ≤ 8 years of age) were administered the EFV oral solution derived from the following formula: dose = (weight in kg/70)0.7 • 720 mg. Eighteen (18) subjects in Cohort II-Stratum 2 (≥ 2 years to ≤ 8 years of age) treated with the EFV oral solution had evaluable EFV PK at Week 2. Of those 18 subjects, 4 (22%) were within the target EFV AUC range. Eleven (11) subjects (61%) had an EFV AUC < 190 µM•h while 3 subjects (17%) had an EFV AUC > 380 µM•h. The mean EFV Cmax, Cmin, and AUC(TAU) at Week 2 were 4.6 µg/mL, 2.5 µg/mL, and 268 µM•h, respectively. A comparison of the PK parameters between subjects 8 years of age or younger on the EFV oral solution (Cohort II-Stratum 2) and on the EFV capsule (Cohort I) demonstrated similar mean Cmax, Cmin, and AUC values (Table 7). However, oral clearance was higher for subjects treated with the oral solution relative to the capsule. The summary statistics for subjects on the oral solution (Cohort II-Stratum 2) included 2 subjects with high clearance values relative to the remaining subjects, which may have impacted the mean value reported. The lower bioavailability of the EFV oral solution relative to the capsule required that a higher dose of the oral solution be administered, contributing to the higher oral clearance values observed in subjects receiving the oral solution. Mean EFV exposures appeared somewhat higher in subjects receiving the EFV oral solution relative to adults treated with the EFV capsule; however exposures were more variable in pediatric subjects receiving the oral solution.

Table 7: Efavirenz PK Parameters in HIV-Infected Pediatric Subjects (8 Years of Age and Younger in Cohort I and Cohort II-Stratum 2) and Adult Subjects After 2 Weeks of Treatment

PK Parameter		Children: Oral Solution (N = 18)	Children: Capsule (N = 29)	Adults: Capsule (N = 35)
Cmax (µM)	Mean (SD)	14.7 (14.9)	15.1 (5.8)	12.9 (3.7)
Cmin (µM)	Mean (SD)	8.0 (13.2)	5.2 (3.4)	5.6 (3.2)
AUC(TAU) (µM•h)	Mean (SD)	268 (317)	216 (91)	184 (73)
CLT/F (L/h/kg)	Mean (SD)	1.08 (2.3)	0.21 (0.08)	NR

Sponsor's csr-final.pdf, pg 10

CONCLUSIONS:

- The pharmacokinetics of EFV in pediatric subjects between the ages of 3 and 16 years of age treated with the capsule formulation (600 mg per day adjusted to body size using the surface rule) are similar to adults treated with 600 mg capsules daily.
- The pharmacokinetics of EFV in pediatric subjects between the ages of 3 and 8 years of age treated with the oral solution formulation at a starting dose of 720 mg per day (adjusted to body size) are similar to adults treated with 600 mg capsules daily. Efavirenz exposures in pediatric subjects 2 years of age or younger after treatment with the oral solution were lower relative to older children receiving the oral solution and adults receiving the capsule.

Pharmacometrics Review

1 Summary of Findings

1.1 *Key Review Questions*

The purpose of this review is to address the following key questions.

1.1.1 Do the results of ACTG382, AI266922, and PACTG1021 support the applicant's proposed dosing recommendations in pediatrics 3 months to ≤ (b) (4) year (and (b) (4) kg to <10 kg)?

Yes, the sponsor's proposed dosing for pediatrics 3 months to ≤ (b) (4) years of age is acceptable. This dosing includes extension of the 200 mg efavirenz dosing increment down to 7.5 kg, a dose of 150 mg efavirenz for pediatrics 5 to 7.5 kg, and a dose of 100 mg efavirenz for pediatrics (b) (4) to 5 kg. For the 100 mg dose, a decision was made to restrict the lower weight range to 3.5 kg based on the following items: i) on increased exposures in such pediatrics with the proposed dosing; ii) restrictions on dosing at lower weights which can only go in 50 mg increments; iii) no pediatrics in the studied population with body weight less than 3.1 kg; and iv) demographic information for pediatrics 3 months of age which supports that few such pediatrics of at least 3 months of age weight less than 3.5 kg. Additional details regarding the dose selection and justification for the adjustment in the body weight cut off are described below.

The sponsor developed a population pharmacokinetic model based on data from the three trials in HIV-1 infected pediatrics (ACTG382, PACTG1021, and AI266922) and a fourth trial in healthy volunteers evaluating the bioavailability of 'sprinkled' efavirenz when administered with various vehicles compared to efavirenz administered as a capsule (fasted). 'Sprinkled' efavirenz refers to the sponsor's final age appropriate efavirenz formulation that involves opening efavirenz capsules/tablets and mixing the contents with an acceptable vehicle (grape jelly, applesauce, yogurt) for administration to the subject. This pediatric formulation was ultimately selected due to lower than acceptable exposures from previous attempts at an age appropriate efavirenz formulation (i.e., solution which was used in a subset of subjects in PACTG1021 and AI266922). Pediatrics were only administered 'sprinkle' efavirenz in AI266922, though both ACTG382 and PACTG1021 contribute pediatric subjects administered efavirenz as either tablets or capsules. The final dataset included 168 pediatric subjects (3289 observations) and 24 adult subjects (1232 observations).

The applicant's final population pharmacokinetic model was used to obtain predictions of AUC_{ss}, C_{min}, and C_{max} for pediatrics <10 kg. While pediatric subjects were dosed at 400-600 mg initially if they had started on efavirenz oral solution or 300 mg efavirenz when initiating efavirenz treatment using 'sprinkles' in AI266922, the exposures observed in these pediatric subjects typically exceeded the upper range of the targeted adult exposure (380 µM·h). This was supported by the sponsor's modeling and simulation results which supports that pediatric doses of 200, 150, and 100 mg for pediatrics ≥7.5 to <10 kg, ≥5 to <7.5 kg, and ≥ (b) (4) to 5 kg, respectively, are predicted to achieve pediatric exposures within the targeted adult AUC range specified in the label (190 to 380 µM·h) (additional PK targets were evaluated but were considered secondary to AUC; C_{max}: 5.2 to 8.2 µg/mL; C_{min}: 1.9 to 2.9 µg/mL). Median (25^{th} and 75^{th} percentile) predictions from the sponsor's population pharmacokinetic model are shown below (Table). Initial steps evaluated by the sponsor use predicted efavirenz exposures for the <10 kg pediatric weight bands assuming all pediatrics would be administered 200 mg q.d (i.e., pediatrics (b) (4) to 10 kg administered 200 mg q.d.) Other scenario considerations included evaluating 150 mg q.d. for (b) (4) kg to 7.5 kg and 100 mg from (b) (4) kg to 5 kg. These results, summarized below, along with predictions for pediatrics >10 kg demonstrate that efavirenz 200 mg q.d. results in AUC exposures within the targeted interval for pediatrics 7.5 kg to 10 kg (predicted median [25^{th}; 75^{th} percentile] mean AUC from 1000 simulated trials: 284 [254; 321] µM·h). However, 200 mg was predicted to result in efavirenz AUC of 350 [309; 465] and 480 [405; 566] µM·h, respectively, exceed the specified upper limit of exposures. Due to the predicted higher exposure with this dosing, alternative regimens were explored in these pediatrics weight ranges and summarized in the same table. It was identified that efavirenz 150 mg q.d. was most

appropriate in pediatric subjects 5 kg to 7.5 kg in order to achieve the targeted adult exposures (263 [233; 303] µM·h) while efavirenz 100 mg q.d. was most appropriate for pediatrics subjects (b) (4) kg to 5 kg (237 [202; 281] µM·h).

Table 1. Simulated Efavirenz Mean AUC Using Capsules/Sprinkles from 1000 Simulated Trials

Body Weight	EFV dose (mg)	AUC (25th; 75th)	[10th to 90th]
>= (b) (4) to <5	100	237 (202; 281)	[177; 331]
>=(b) (4) to <5	*150*	*359 (303; 424)*	*[267; 508]*
>=(b) (4) to <5	*200*	*480 (405; 566)*	*[356; 678]*
>=5 to <7.5	150	263 (233; 303)	[207; 347]
>=5 to <7.5	*200*	*350 (309; 465]*	*[277; 465]*
>=7.5 to <10	200	284 (254; 321)	[230; 364]
>=10 to <15	200	238 (216; 263)	[199; 289]
>=15 to <20	250	234 (215; 258)	[198; 285]
>=20 to <25	300	257 (238; 278)	[223; 309]
>=25 to <32.5	350	262 (241; 294)	[225; 325]
>-32.5 to <40	400	259 (242; 284)	[225; 314]
>=40	600	255 (228; 291)	[207; 323]

Sponsor's pediatric-m-s-ppk-report.pdf, pg 83 and 84.

A similar table for the proposed pediatric dosing including predicted efavirenz C_{max} and C_{min} values is shown below (Table 2). These predicted C_{max} and C_{min}values fall within the specified efaviranz values for these pharmacokinetic parameters (C_{max}: 5.2 to 8.2 µg/mL; C_{min}: 1.9 to 2.9 µg/mL) and further support the proposed efavirenz dosing.

Table 2. Simulated Efavirenz Mean AUC, C_{max}, and C_{min} Using Capsules/Sprinkles from 1000 Simulated Trials

Body Weight	EFV dose (mg)	AUC (25th; 75th)	Cmax (25th; 75th)	Cmin (25th; 75th)
>=(b) (4) to <5	100	237 (202; 281)	6.2 (5.3; 7.3)	2.6 (2.2; 3.2)
>=5 to <7.5	150	263 (233; 303)	7.1 (6.3; 8.1)	2.7 (2.3; 3.3)
>=7.5 to <10	200	284 (321; 254)	7.8 (7.0; 8.8)	2.9 (2.5; 3.4)
>=10 to <15	200	238 (216; 263)	6.5 (6.0; 7.2)	2.3 (2.1; 2.7)
>=15 to <20	250	234 (215; 258)	6.5 (6.0; 7.1)	2.3 (2.0; 2.6)
>=20 to <25	300	257 (238; 278)	7.0 (6.6; 7.6)	2.6 (2.3; 2.9)
>=25 to <32.5	350	262 (241; 294)	7.1 (6.5; 7.9)	2.7 (2.4; 3.1)
>-32.5 to <40	400	259 (242; 284)	7.0 (6.5; 7.7)	2.7 (2.4; 3.0)
>=40	600	255 (228; 291)	6.6 (6.0; 7.5)	2.8 (2.5; 3.3)

Sponsor's pediatric-m-s-ppk-report.pdf, pg 83-86.

Overall, the applicant's selected efavirenz dosing was found to be acceptable. However, there were concerns regarding efavirenz exposure in pediatrics <3.5 kg who would be administered efavirenz 100 mg q.d. This concern was based on a higher predicted mean efavirenz C_{max} and AUC in pediatrics (b) (4) to 3.5 kg, the higher mg/kg the would be administered in such subjects (40 to 28.6 mg/kg), concerns regarding the administration volume in the population, that 3.3 kg was the lowest body weight included in

the trial (administered oral solution) and the lowest body weight pediatric administered sprinkles was 4.1 kg, and that the 5th percentile body weight for a 3 month old pediatric subject (US CDC growth charts, female) is 4.5 kg. It was anticipated that providing dosing recommendations to a lower body weight than 3.5 kg may imply treatment is permissible in pediatrics <3 months of age. For additional details on pediatric growth charts from other countries see the review from the medical officer (Dr. Shapiro).

1.2 *Recommendations*

The application is approvable from a Pharmacometrics perspective. There are no requested Phase IV commitments

1.3 *Label Statements*

(b) (4)

Table 1: SUSTIVA Dosing in Pediatric Patients at least 3 months old

Patient Body Weight	SUSTIVA Daily Dose	Number of Capsules or Tablets and Strength to Administer
3.5 kg to less than 5 kg	100 mg	(2) 50 mg capsules
5 kg to less than 7.5 kg	150 mg	(3) 50 mg capsules
7.5 kg to less than 15 kg	200 mg	(1) 200 mg capsule
15 kg to less than 20 kg	250 mg	(1) 200 mg + (1) 50 mg capsule
20 kg to less than 25 kg	300 mg	(1) 200 mg + (2) 50 mg capsules
25 kg to less than 32.5 kg	350 mg	(1) 200 mg + (3) 50 mg capsules
32.5 kg to less than 40 kg	400 mg	(2) 200 mg capsules
at least 40 kg	600 mg	(1) 600 mg tablet* OR (3) 200 mg capsules

2 Pertinent regulatory background

Efavirenz (EFV), approved in the US and marketed as Sustiva® by the applicant, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of human immunodeficiency virus (HIV) type-1 infection in combination with other antiretroviral agents. The recommended adult dosage for EFV is 600 mg once daily. EFV, in combination with 2 nucleoside reverse transcriptase inhibitors, is also an approved treatment naïve regimen for children ≥ 3 years of age based on clinical trial experience. The use of EFV is approved for pediatric HIV-1 patients at least 3 years of age and weighing at least 10 kg, but it is not approved for children < 3 years of age.

This submission provides data and recommendations to support a proposed expansion of the pediatric indication for EFV to include HIV-1 patients 3 months to 3 years of age and weighing at least (b) (4) kg, using a "capsule sprinkle" method of administration (contents of the open capsule sprinkled into a small amount of food or formula) to dose children that are not able to swallow intact capsules. This submission includes data from 3 pediatric dose-ranging studies, providing experience with EFV across a total of 182 children between the ages of 3 months (90 days) and 21 years. Efficacy, safety, and pharmacokinetic data from each of the dose-ranging studies, as well as modeling and simulation data, adult bioavailability data comparing intact capsules to capsule contents mixed with a small amount of food (capsule-sprinkle), and supplemental safety information from expanded access programs are also being used to support the proposed pediatric dosing strategy.

3 Results of Sponsor's Analysis

3.1 *Introduction*

Details on the three pediatric studies and the adult bioavailability study used to support this submission are described in detail in the Individual Study section of the QBR. The Pharmacometrics Review focuses on review and assessment of the population pharmacokinetic modeling and simulation report that is used to support the applicant's proposed doses.

3.2 *Population Pharmacokinetic Model*

Report 5.3.3.5: Population Pharmacokinetic Analysis of Efavirenz (BMS-561525) in Pediatric Patients

The purpose of this project was to develop a population pharmacokinetics model to describe efavirenz concentration-time profiles in pediatric patients infected with HIV-1. The analysis would include an investigation of the effects of covariates on efavirenz PK parameters and modeling and simulation to support dose recommendations of efavirenz capsule sprinkle in pediatrics 3 months to 18 years.

3.2.1 Data

The PPK analysis utilized PK data collected in pediatric HIV patients between 3 months and 21 years of age (Studies PACTG 382, PACTG 1021, and AI266922) at the initiation of treatment. To minimize influence by the adult data, it was intended to mainly use pediatric data for model development. During the course of the analysis, the US Food and Drug Administration (FDA) recommended the inclusion of Study AI26659 in order to provide additional PK data, as capsule sprinkles were used in this study and this study provides frequent PK sampling. AI266059 was conducted to evaluate the relative bioavailability between capsule and capsule sprinkle formulations, as well as the impact of the type of food mix-ins with capsule sprinkles for pediatric administration. Brief summaries of each study that was included in this analysis (PACTG 382, PACTG 1021, and AI266922) are provided below inTable 3.

Table 3: Summary of Clinical Studies Used in the Population Pharmacokinetic Analysis

Study	Study Population	Study Design	Study Drug Dosage Regimens	# of Planned Patients	Nominal PK Assessments
PACTG 382	Pediatric HIV	A Phase 1/2 open-label, multicenter, AUC-controlled study to determine the PK, safety, tolerability, and efficacy in children Cohort I: 57 children 3 to 16 years Cohort II: 45 children Stratum 1 - 3 months to < 2 years Stratum 2 - 2 to 8 years	Cohort I: capsule, starting dose = (wt/70)$^{0.7}$ x 600 mg, max 1000 mg/daily for 208 wks Cohort II: solution, starting dose = (wt/70)$^{0.7}$ x 720 mg, max 1000 mg/daily, for 208 wks	45	Cohort I: Intensive sampling on Weeks 2, 6, (10), 56, and 112 at 0, 2, 3-6, 8, 12, 24 hr post-dose Cohort II: Intensive sampling on Weeks 2, (6), 56, and 112 at 0, 2, 3-6, 8, 12hr post-dose
PACTG 1021	Pediatric HIV	An open-label study to evaluate the safety, tolerance, antiviral-activity and PK. Group 1: 6 children 3 months to < 3 years Group 2: 21 children 3 to 12 years Group 3: 16 children 13 to 21 years	Group 1: Initial doses given as solution, capsule dispersal used when AUC below threshold value, starting solution dose: 190 mg (<10 kg), 600 mg (10 to <32.5 kg), for 96 wks Groups 2 and 3: oral solution or capsule, starting solution dose: 360 mg (10 to < 15 kg), 390 mg (15 to < 20 kg), 450 mg (20 to < 25 kg), 510 mg (25 to < 32.5 kg), 630 mg (32.5 to < 40 kg), 720 (≥ 40 kg) for 192 wks	43	Intensive sampling on Weeks 2 and 12 with sampling times at 0, 3, 5, 10, and 24 hr post-dose (Group 1) or 0, 1, 2, 4, 8, 12, and 24 hr post dose (Groups 2 and 3) Additional intensive sampling after formulation changes and after dose adjustment
AI266922	Pediatric HIV	A Phase 2 open-label, multicenter study of liquid and sprinkled formulations of EFV Group 1: 12 infants, 3 months to < 6 months Group 2: 10 infants, 6 months to < 2 years Group 3: 4 children, 2 to < 3 years Group 4: 6 children, 3 to 6 years	Groups 1 - 3: oral solution prior to Amendment 03, capsule as a sprinkle preparation after Amendment 03, starting solution dose: 390 mg (< 10 kg), 600 mg (10 to 17 kg), for 48 wks and reaches 3 years Group 4: oral solution, starting solution dose: 360 mg (10 to < 15 kg), 390 mg (15 to < 20 kg), 450 mg (20 to < 25 kg), 510 mg (25 to < 32.5 kg), 630 mg (32.5 to < 40 kg), 720 (≥ 40 kg) for 48 wks	32	Intensive sampling on Weeks 2, 10, and 18 with sampling times at 0, 0.5, 1, 3, 5, 8, and 24 hr post-dose Additional intensive sampling after formulation changes from solution to sprinkle or after dose adjustment
AI266059	Adult Healthy	An open-label, randomized, 3-period, 3-treatment crossover study design to assess bioavailability of EFV capsule contents mixed with food vehicles (applesauce, grape jelly, or yogurt) or baby formula relative to the intact capsule formulation administered under fasted conditions	Treatment A: 600 mg intact capsule (fasted). Treatment B: 600 mg capsule contents mixed with 2 teaspoons of Mott's natural applesauce. Treatment C: 600 mg mixed with 2 teaspoons of Smucker's concord grape jelly. Treatment D: 600 mg mixed with 2 teaspoons of Stonyfield Farm organic whole milk plain yogurt. Treatment E: 600 mg mixed with 2 teaspoons of Enfamil with iron baby formula.	24	Intensive sampling over a 21-day period after dosing at the following approximate times during each of the 3 study periods, prior to dosing (0 hour), and at 1, 2, 3, 4, 5, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 336, and 480 hours following dose administration.

Source: Sponsor's population PK report, pg 19

For the model development dataset, pooled NONMEM compatible datasets were created from datasets (PACTG 382, PACTG 1021, AI266922, and AI266059) received from BMS. The pooled NONMEM-ready PK dataset contained derived actual sample collection time relative to previous dose, dose amount, formulation, week of treatment, and demographic information merged with the PK exposure data. For the model development, samples with missing dose information immediately prior to the sample collection time were excluded from the model development dataset (13 samples). Samples with duplicate assay results reported at the same collection time were excluded from the model development dataset. All pre-dose concentration values on Study Day 1 were excluded from the model development dataset. PK measurements determined to be below the limit of quantification (BLQ) were excluded from the analysis, as the number of BLQ samples were small A total of 3,289 concentration records were collected from 168 pediatric patients (PACTG 382, PACTG 1021, and AI266922) in the PPK analysis dataset, while AI266059 provided an additional 1,232 concentration records from 24 adult healthy volunteers (Table 4).

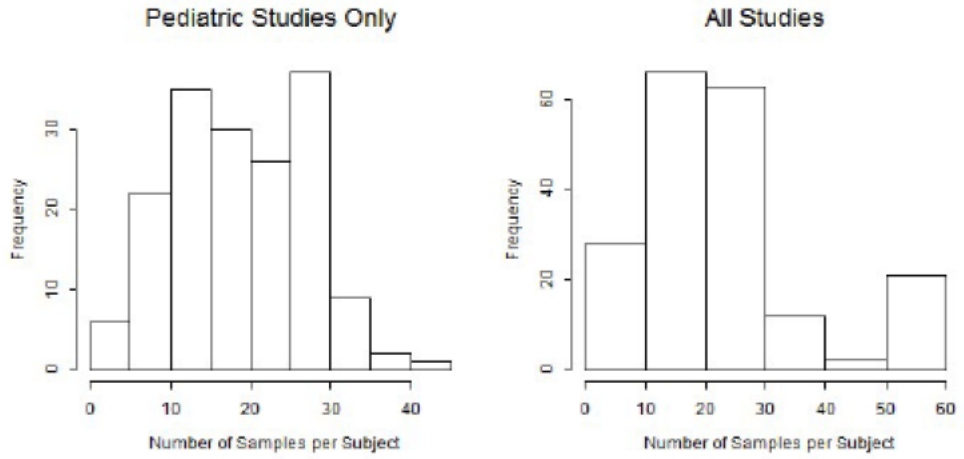
Table4: Analyses Dataset Details

Study	Formulation[a]	No. Subjects Included[b]	No. Samples Included	Total No. of Samples by Study
PACTG 382	Capsule	93	1210	1772
	Solution		562	
PACTG 1021	Capsule	41	548	828
	Solution		280	
AI266922	Capsule	34	342	689
	Solution		347	
AI266059	Capsule	24	1232	1232
Total		192	4521	

Source: Sponsor's population PK report, pg 28

Figure 6 presents the number of samples per subject in the updated dataset. Median number of samples per patient in the pediatric trials was 20, and the number of samples per patient ranged from 4 to 42 samples.

Figure 6: Histograms of Number of Samples per Subject in the Updated Dataset



Source: Sponsor's population PK report, pg 30

Individual subject demographics are summarized inTable 5.

Table 5: Summary of Demographic Characteristics by Study for Pediatric Subjects in the Updated Dataset

Covariate	Statistic	PACTG 382	AI266922	PACTG 1021
N	168	93	34	41
N of Dosing	928	299	295	334
N of Dosing Per Patient	5.5	3.2	8.7	8.1
Age (years) at Baseline	Mean ± SD	5.71 ± 4.02	1.67 ± 1.67	9.92 ± 6.77
	Median (min, max)	5.5 (0.2,16.9)	0.725 (0.29,6.98)	8.75 (0.31,21.1)
Age (years) at Dosing	Mean ± SD	6.53 ± 4	3.02 ± 1.92	10.3 ± 6.81
	Median (min, max)	6.25 (0.2,19.4)	2.78 (0.29,7.9)	9.02 (0.31,24.7)
Weight (kg) at Dosing	Mean ± SD	23.2 ± 14.2	12.3 ± 3.99	38.9 ± 27.4
	Median (min, max)	20.5 (4.9,98.2)	12.5 (3.3,23)	26.6 (4.6,117)
Gender				
Male	N (%)	37 (39.8)	22 (64.7)	21 (51.2)
Female	N (%)	56 (60.2)	12 (35.3)	20 (48.8)
Race				
White	N (%)	25 (26.9)	22 (64.7)	9 (22)
Black/ African American	N (%)	55 (59.1)	7 (20.6)	26 (63.4)
Asian	N (%)	0	0	0
Other	N (%)	13 (14)	5 (14.7)	6 (14.6)

Source: Sponsor's population PK report, pg 34

3.2.2 Methods

The population PK model was developed in steps; a base model for description of structural components of the model, a full model including all of the pre-specified covariate effects of interest, then the final model chosen by retaining only the statistically significant covariate effects. The parameters in the population models were estimated using the NONMEM (version VI or higher).

The first-order conditional estimation method was used for estimation. A 2-compartment model with first-order absorption and first-order elimination was used as the base model. Then, a full covariate model was developed using pre-specified covariates, including age, weight, gender, race, and formulation. In addition, previous antiviral therapy and co-medication with protease inhibitor (PI) was explored. The full model underwent the Wald's approximation method (WAM) procedure and backward elimination to identify a parsimonious final model that contained covariates that were statistically significant.

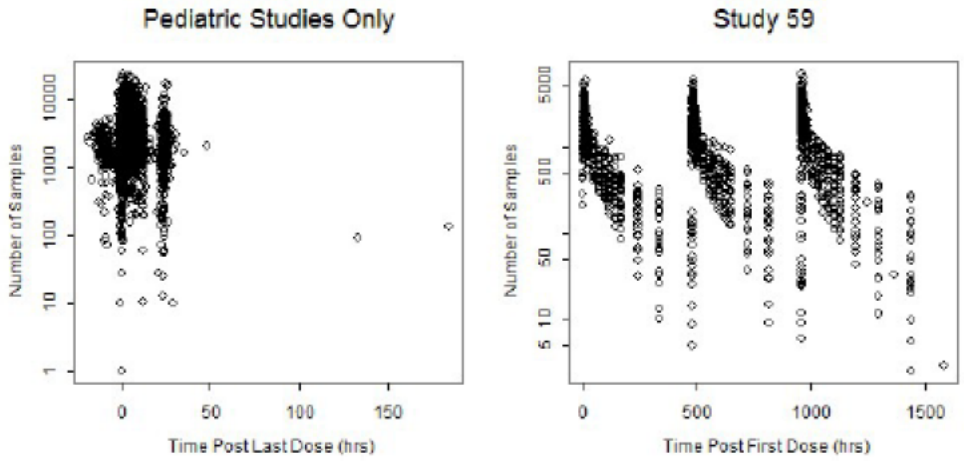
The final population PK model with the updated dataset was used to simulate steady-state efavirenz concentration-time curves at various dose regimens for the capsule sprinkle or capsule formulation in pediatric patients. This was to find dose regimens that produced comparable exposure between the pediatric patients with weight <10 kg and pediatrics ≥10 kg (already approved regimens). The exposure measures used included area under the concentration-time curve in 24 hours at steady state (AUC_{ss}), maximum observed plasma concentration (C_{max}), and pre-dose concentration at steady state, or C_0. The current US label states that the current pediatric dosing recommendations target AUC levels in the range of 190-380 μM•h. However, there are no pre-defined references for C_{max} and C_0; thus, simulated C_{max} and C_0 values for pediatrics 10-40 kg served as the references
Following completion of the final pediatric model evaluation and simulations, an exploratory assessment of the impact of relevant CYP450 SNPs on EFV clearance was performed. The pharmacogenomic information was limited and available for 28 subjects from AI266922 only.

3.2.3 Results

3.2.3.1 Observed Concentration-Time Profiles

Figure 7presents concentration vs. time plots.

Figure 7: Concentration Versus Time After the Last Dose (Left for Pediatric Data) and Time Since the First Dose (Right for Adult Data) in the Updated Dataset



Source: Sponsor's population PK report, pg 32

3.2.3.2 Population PK Model Results

The population PK of efavirenz in the pediatric population were well described by a first-order absorption and 2-compartment disposition model. Given the sampling schemes of the pediatric studies, parameters describing the distribution phase with the pediatric studies alone were not well estimated. The adult study data provided information on the distribution and absorption phases for the pediatric data, and k_a, Q, and V_3 were shared among the adult and pediatric populations.

Diagnostic plots with the initial base model indicated differences between capsule sprinkles and oral solution. Oral solution demonstrated lower bioavailability relative to capsule sprinkles, and the degree of lowered bioavailability with oral solution was different from study to study. For this reason, the effect of significant formulation was included as part of the base structural model. The solution formulation showed higher residual variability that warranted a specific parameter for the residual model. Given the established bioequivalence between capsules and capsule sprinkles with food mix-ins in AI266059, capsule and capsule sprinkles were treated as the same formulation in the analysis.

For the inter-individual random effects, several structural forms were explored including unstructured, banded, block(CL, V_2) and block(Q, V_3), and block(CL, V_2). Although some of these runs were successful, off-diagonal elements were not well estimated in general, which could have caused issues during the simulation for dose recommendations later. For that reason, the final base model included a diagonal structure. The final base model included a parameter for absorption lag-time for the adult data.

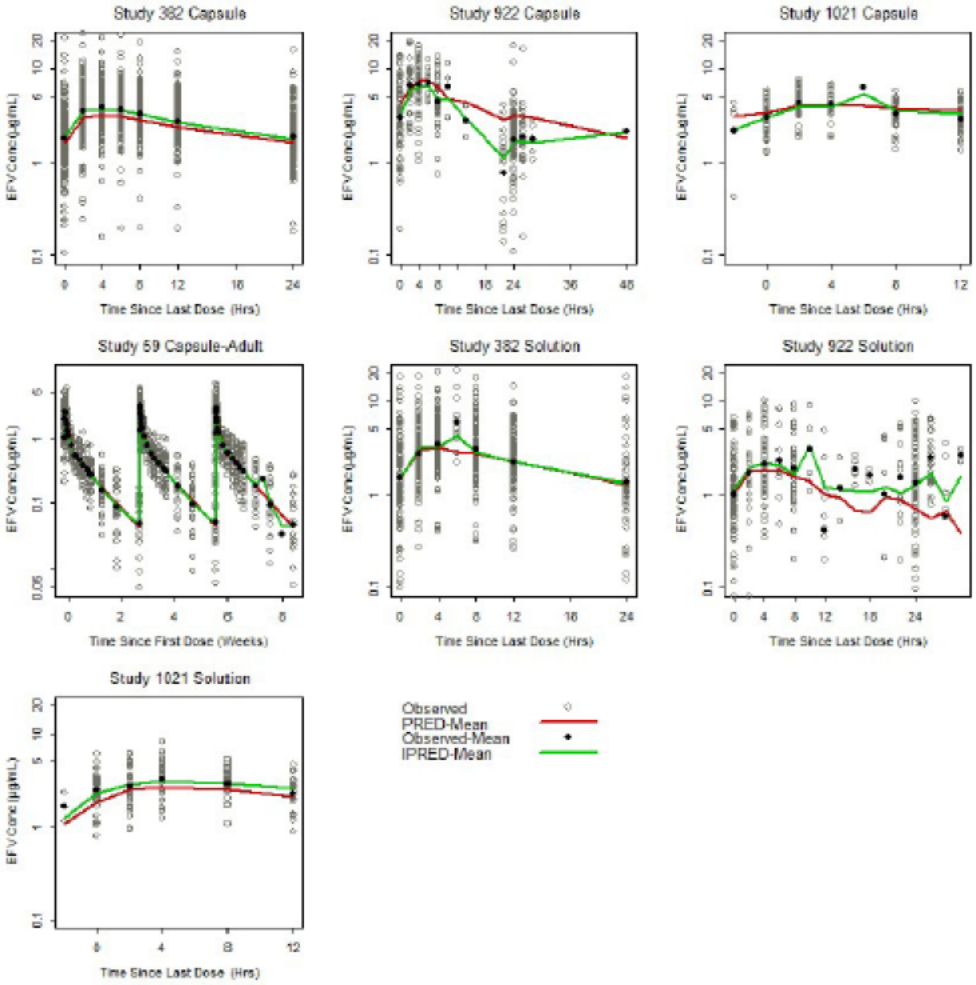
A full model was constructed with pre-specified covariate effects. The full covariate model was successfully developed, including age, weight, gender, race, previous antiviral therapy (indicator of PACTG 1021) and co-medication of PI (indicator of PACTG 382). Both of the WAM and backward elimination methods were in agreement, and selected weight on clearance, weight on central volume, and weight on rate of absorption, and previous antiviral therapy on clearance. As previous antiviral therapy was by the study design of PACTG 1021, it is unclear whether this effect was confounded by the study effect. A summary of the parameter estimates for the base, full, and final models are shown in Table 6. The structural parameter estimates were consistent across the model. The final model had 5 fewer parameters, while the OFV was only 5.4 points higher than the full model. Figure 8 presents the model fit of the final model.

Table 6: Parameter Estimates of Base, Full, and Final Models

Parameter [Units]		Estimate ± SE		
		Base	Full	Final
	OFV	-2252.197	-2478.589	-2473.174
		Fixed Effects		
CL/F_1 [L/h]	θ_1	4.87±0.347	5.67±1.15	4.85±0.347
WT [kg]	θ_{15}	--	0.673±0.23	0.619±0.114
AGE [yr]	θ_{18}	--	-0.0201±0.136	--
SEX	θ_{20}	--	-0.0906±0.0963	--
Race-Black	θ_{21}	--	0.135±0.14	--
Race-Other	θ_{22}	--	-0.0781±0.128	--
PINT	θ_{23}	--	-0.199±0.165	--
PART	θ_{24}	--	-0.458±0.155	-0.315±0.111
V2/ F_1 [L]	θ_2	22.6±4	91.3±8.86	91.6±9.2
WT [kg]	θ_{16}	--	1.39±0.176	1.41±0.164
Q/F_1 [L/h]	θ_3	7.64±1	5.47±0.753	5.44±0.736
V3/F_1 [L]	θ_4	425±40.2	286±33.6	286±33.5
Ka	θ_5	0.11±0.0107	0.431±0.05	0.444±0.0421
WT [kg]	θ_{17}	--	0.817±0.396	0.653±0.0966
AGE [yr]	θ_{19}	--	-0.115±0.251	--
Relative F_1 for solution – Study 382	θ_{10}	-0.169±0.112	-0.355±0.0896	-0.339±0.0857
Relative F_1 for solution – Study 922	θ_{11}	-0.693±0.0646	-0.753±0.0532	-0.756±0.0493
Relative F_1 for solution – Study 1021	θ_{12}	-0.269±0.0977	-0.52±0.0938	-0.49±0.0893
CL/F_1 [L/h] – adult	θ_7	3.67±0.299	3.66±0.297	3.66±0.297
V2/F_1 [L] – adult	θ_8	16.1±2.84	186±15	186±15.1
Tlag [h] - adult	θ_{14}	0.618±0.0402	0.62±0.0383	0.619±0.0378
		Interindividual (IIV) Random Effects		
IIV_CL	$\omega_{1,1}$	0.65	0.609	0.619
IIV_V2	$\omega_{2,2}$	0.539	0.494	0.499
IIV_Q	$\omega_{3,3}$	0.822	0.9	0.906
IIV_V3	$\omega_{4,4}$	0.434	0.544	0.546
IIV_Ka	$\omega_{5,5}$	0.504	0.431	0.418
IIV_CL (adult)	$\omega_{6,6}$	0.399	0.397	0.397
IIV_V2 (adult)	$\omega_{7,7}$	0.575	0.363	0.362
		Residual Error Random Effects		
capsule - pediatrics	θ_6	0.449±0.0303	0.432±0.0287	0.433±0.0288
solution	θ_{13}	0.667±0.0646	0.662±0.0632	0.662±0.063
adult	θ_9	0.212±0.00866	0.212±0.00864	0.212±0.00864

Source: Sponsor's population PK report, pg 69-70

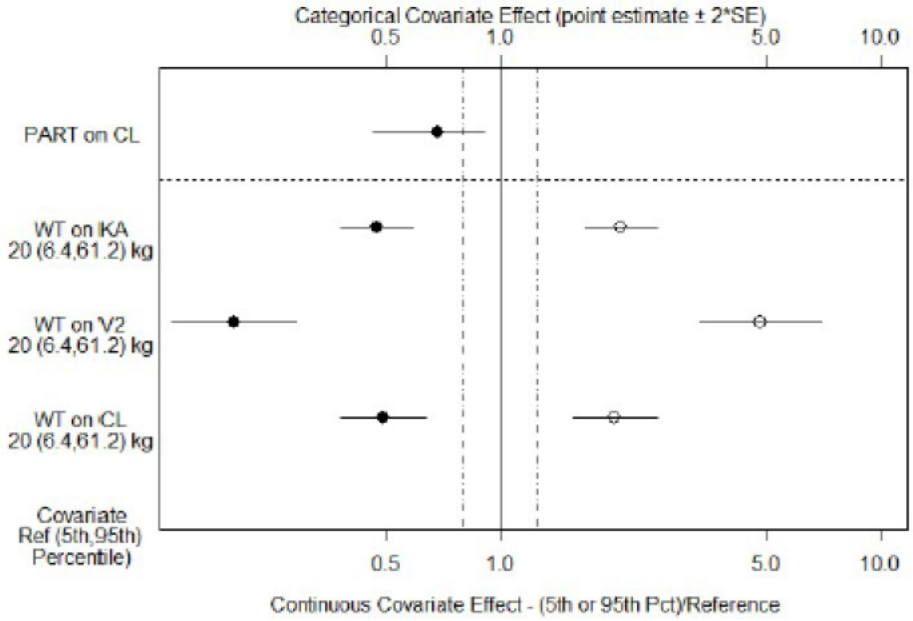
Figure 8: Goodness of Fit of Final Model: Observed (DV), Individual Predicted (IPRED), and Population Predicted (PRED) Concentrations vs. Time



Source: Sponsor's population PK report, pg 68

The graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters are presented in Figure 9. The estimated covariate effects are represented as the ratio of typical parameters at reference values of the covariates. All the weight covariate effects have the effect magnitude falling outside (b) (4) reference value, suggesting weight may be clinically relevant. The status of previous antiviral therapy (PACTG 1021 by design) showed a statistically significant effect; however, the upper confidence level of the magnitude was greater than (-0.2), which is inconclusive about clinical importance.

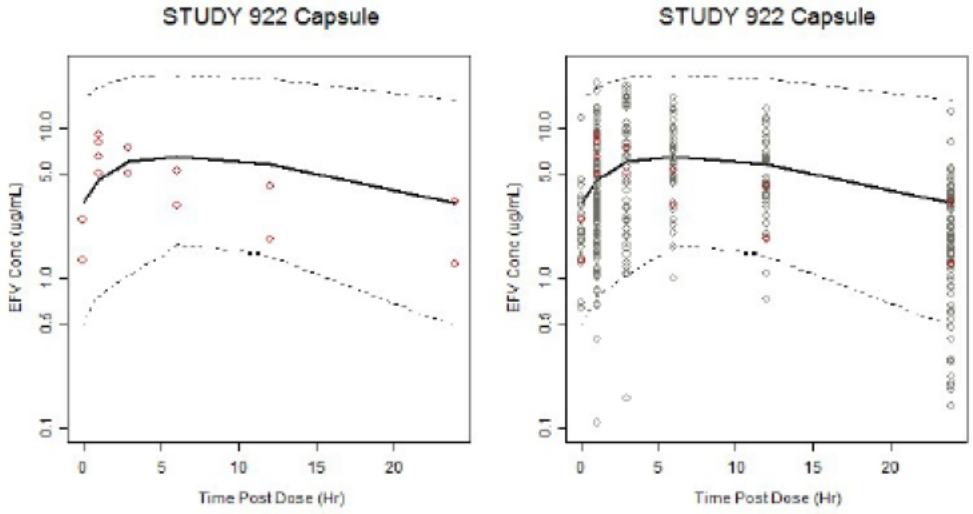
Figure 9: Effect of Continuous/Categorical Covariates on PK Parameters

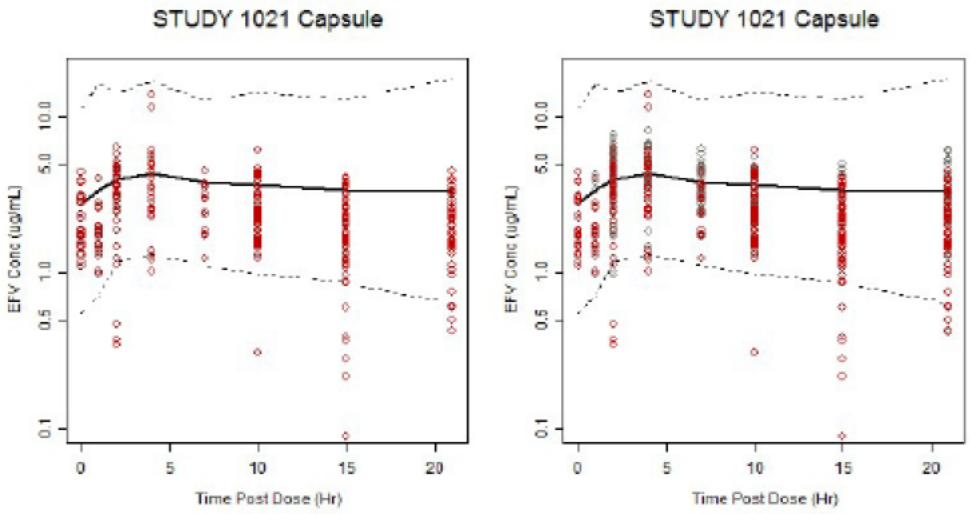


Source: Sponsor's population PK report, pg 71

The NONMEM ready dataset was revised after model development was completed. Using the updated dataset, an external model validation via PPC was performed; the final model was used to simulate the observed study designs using the updated dataset. Then, the simulated data were overlaid with the observed updated dataset (Figure 10). Overall, the newly added samples appear to be contained in the simulated distribution, indicating that the exposure predicted by the final model built on the model development dataset was comparable to the observed exposure.

Figure 10: External PPC Results –Study AI266922 Capsules and PACTG 1021 Capsules





Source: Sponsor's population PK report, pg 75-76

Given the consistency of the newly added data to the final model, no new model development was performed using the updated dataset. Only the base and final models were re-run using the updated dataset to update parameter estimates. Due to a >15% change in CL with inclusion of outlier in the analyses, outlier measurements were removed according to the analysis plan. The updated dataset without the outliers was used to update the parameter estimates of the final model (Table 7). The CL estimate was almost identical (< 1% difference) between the model development dataset and the updated dataset. The V2 estimate was 7% lower with the updated dataset. Other parameter estimates were generally comparable, with the exception of the effect of previous ARV therapy and the relative bioavailability of PACTG 1021 oral solution.

Table 7: Parameter Estimates of Final Models with the Model Development Dataset and the Updated Dataset

Parameter [Units]		Estimate ± SE	
		Model Development Dataset	Updated Dataset
CL/F$_1$ [L/h]	θ_1	4.85±0.347	4.8±0.33
WT [kg]	θ_{15}	0.619±0.114	0.57±0.107
AGE [yr]	θ_{18}	--	--
SEX	θ_{20}	--	--
Race-Black	θ_{21}	--	--
Race-Other	θ_{22}	--	--
PINT	θ_{23}	--	--
PART	θ_{24}	-0.315±0.111	0.381±0.401
V2/ F$_1$ [L]	θ_2	91.6±9.2	84.9±8.13
WT [kg]	θ_{16}	1.41±0.164	1.35±0.152
Q/F$_1$ [L/h]	θ_3	5.44±0.736	6.01±0.839
V3/F$_1$ [L]	θ_4	286±33.5	287±34.4
Ka	θ_5	0.444±0.0421	0.414±0.0387
WT [kg]	θ_{17}	0.653±0.0966	0.768±0.0844
AGE [yr]	θ_{19}	--	--
Relative F$_1$ for solution – Study 382	θ_{10}	-0.339±0.0857	-0.346±0.0803
Relative F$_1$ for solution – Study 922	θ_{11}	-0.756±0.0493	-0.754±0.0518
Relative F$_1$ for solution – Study 1021	θ_{12}	-0.49±0.0893	-0.0509±0.344
CL/F$_1$ [L/h] – adult	θ_7	3.66±0.297	3.66±0.294
V2/F$_1$ [L] – adult	θ_8	186±15.1	188±14.9
Tlag [h] - adult	θ_{14}	0.619±0.0378	0.633±0.0357
Interindividual (IIV) Random Effects			
IIV_CL	$\omega_{1,1}$	0.519	0.776
IIV_V2	$\omega_{2,2}$	0.499	0.484
IIV_Q	$\omega_{3,3}$	0.906	0.834
IIV_V3	$\omega_{4,4}$	0.546	0.544
IIV_Ka	$\omega_{5,5}$	0.418	0.449
IIV_CL (adult)	$\omega_{6,6}$	0.397	0.397
IIV_V2 (adult)	$\omega_{7,7}$	0.362	0.363
Residual Error Random Effects			
capsule - pediatrics	θ_6	0.433±0.0288	0.461±0.0286
solution	θ_{13}	0.662±0.063	0.784±0.101
adult	θ_9	0.212±0.00864	0.212±0.00862

Source: Sponsor's population PK report, pg 80-81

Reviewer's comments: Overall, the sponsor's population PK model for efavirenz was found acceptable. The reviewer identified the same base model structure and covariates during independent model development and, as such, has left the sponsor's model unchanged.

Body weight was identified as the primary covariate on both clearance and central volume of distribution. Inclusion of body weight as a covariate on intercompartmental clearance or peripheral volume of distribution did not improve model fits; however, the available pediatric data provided minimum information for informing these parameter estimates based on the sampling scheme in the pediatric studies (e.g., these parameters were primarily informed from the adult bioavailability study data). Based on the identified body weight covariate, the use of weight-based cut points for dosing of efavirenz is supported. Similar to the sponsor, the reviewer identified a body weight effect on oral absorption that significantly improved the model fit.

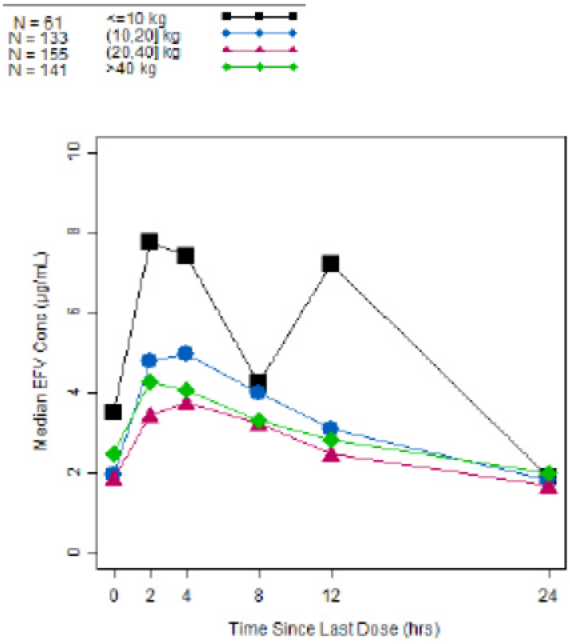
Other covariates identified by the sponsor were also identified during the reviewer's independent analysis. The reviewer agrees that the identified covariate for previous antiviral therapy may have been a study

specific effect and should be interpreted with caution. Likewise, the large parameter change in bioavailability of the oral solution formulation for study PACTG 1021 may be due to the inclusion of multiple additional sparse samples in the update dataset, but is not anticipated to impact model predictions regarding the capsule or capsule sprinkle formulations.

3.2.3.3 Efavirenz Simulations to Support Pediatric Dosing

Weight was found to be a clinically important covariate on EFV exposure. Figure 11 visualizes the effect of weight on EFV exposure using the observed concentration versus time for the 4 weight categories (< 10 kg, ≥ 10 to < 20 kg, ≥ 20 to < 40 kg, and ≥ 40 kg). The observed data suggest that the actual doses in the pediatric trials for the lowest weight group may have been too high, as the observed plasma concentrations in these patients were considerably higher than those in the higher weight bands.

Figure 11: Weight Effect on Median Efavirenz Concentration Versus Time - Actual Dose



Source: Sponsor's population PK report, pg 40

Based on this observation, the final model with the updated dataset was then used for simulations in order to recommend doses for children with weights < 10 kg. Simulated datasets (N=1,000) were created, with each dataset containing 100 pediatric subjects per weight category. For each subject, sampling times of 0, 1, 2, 4, 6, 8, 12, and 24 hours post a steady-state dose were created. Then, parametric bootstrapping was applied using the final PK model. For each simulated dataset, mean individual AUC per dose weight group was calculated, and the distribution of the mean AUC was used to determine the appropriate dose regimen for the corresponding weight category.

Simulation results suggest 200 mg, 150 mg, and 100 mg once daily for [7.5 to 10 kg) (i.e.,.[7.5 to < 10 kg), [5 to 7.5 kg), and (b) (4) to 5 kg), respectively, appear to produce comparable exposure to that of children weighing at least 10 kg and receiving the current approved dosing regimens. These doses produce median AUC in the target range recommended in the US prescribing information and comparable levels to the weight groups of at least 10 kg (Table 8).

Table 8: Simulation Results of Efavirenz Mean AUCss µM•h, 100 Subjects Per Weight Group for Capsules/Capsule Sprinkles, 1000 Simulated Trials – Using Proposed Dose Regimens

Weight (kg)	Dose	10th	25th	50th	75th	90th
≥ (b) (4) to < 5	100 mg	177.32	202.07	237.42	281.44	331.21
≥ 5 to < 7.5	150 mg	206.65	233.38	262.62	302.68	346.76
≥ 7.5 to < 10	200 mg	229.97	254.41	284.28	321.52	364.07
≥ 10 to < 15	200 mg	198.74	216.47	238.14	262.63	289.46
≥ 15 to < 20	250 mg	197.83	215.19	233.98	258.08	285.33
≥ 20 to < 25	300 mg	222.87	238.46	257.56	277.72	309.08
≥ 25 to < 32.5	350 mg	224.87	241.2	262.37	293.98	324.96
≥ 32.5 to < 40	400 mg	224.94	241.94	259.79	283.62	314.01
≥ 40	600 mg	206.53	228.24	254.78	290.65	323.44

Source: Sponsor's population PK report, pg 3

The empirical criteria used was that median C_{max} and C_0 was to be within 80%-125% of reference values, which were the median values from children with weights of 10-15 kg. The reference ranges for C_{max} and C_0 were (5.2, 8.2) and (1.9, 2.9) µg/mL, respectively. The simulation results for C_{max} and C_0 also support the use of 100 mg for (b) (4) to 5 kg, 150 mg for 5 to 7.5 kg, and 200 mg for 7.5 to 10 kg (Table 9 and 10).

Table 9: Simulation Results of Efavirenz Mean C_{max} µg/mL, 100 Subjects Per Weight Group for Capsules/Capsule Sprinkles, 1000 Simulated Trials – Using Proposed Dose Regimens

Weight (kg)	Dose	10th	25th	50th	75th	90th
≥ (b) (4) to < 5	100 mg	4.68	5.32	6.21	7.31	8.49
≥ 5 to < 7.5	150 mg	5.66	6.32	7.07	8.09	9.18
≥ 7.5 to < 10	200 mg	6.42	7.02	7.75	8.79	9.77
≥ 10 to < 15	200 mg	5.55	5.97	6.54	7.18	7.87
≥ 15 to < 20	250 mg	5.59	5.97	6.47	7.13	7.83
≥ 20 to < 25	300 mg	6.17	6.56	7.04	7.61	8.44
≥ 25 to < 32.5	350 mg	6.12	6.53	7.12	7.87	8.69
≥ 32.5 to < 40	400 mg	6.09	6.48	6.96	7.65	8.31
≥ 40	600 mg	5.43	5.93	6.57	7.51	8.32

Source: Sponsor's population PK report, pg 3

Table 10: Simulation Results of Efavirenz Mean C_0 µg/mL, 100 Subjects Per Weight Group for Capsules/Capsule Sprinkles, 1000 Simulated Trials – Using Proposed Dose Regimens

Weight (kg)	Dose	10th	25th	50th	75th	90th
≥ (b) (4) to < 5	100 mg	1.86	2.18	2.62	3.22	3.89
≥ 5 to < 7.5	150 mg	2.04	2.33	2.71	3.28	3.82
≥ 7.5 to < 10	200 mg	2.19	2.48	2.87	3.35	3.88
≥ 10 to < 15	200 mg	1.86	2.06	2.32	2.69	3.05
≥ 15 to < 20	250 mg	1.84	2.02	2.3	2.6	2.96
≥ 20 to < 25	300 mg	2.06	2.28	2.55	2.89	3.26
≥ 25 to < 32.5	350 mg	2.13	2.37	2.68	3.08	3.56
≥ 32.5 to < 40	400 mg	2.18	2.4	2.69	2.99	3.37
≥ 40	600 mg	2.18	2.46	2.82	3.27	3.72

Source: Sponsor's population PK report, pg 4

Reviewer's comments: The efavirenz capsule sprinkle doses originally evaluated in pediatrics <10 kg resulted in exposures exceeding typical exposures exceeding those in pediatrics >10 kg and in adults (Figure 11). These observations, and the sponsor's provided modeling and simulation of efavirenz exposures in pediatrics supports the sponsor's proposed efavirenz doses in pediatrics <10 kg and the already labeled efavirenz doses in pediatrics >10 kg.

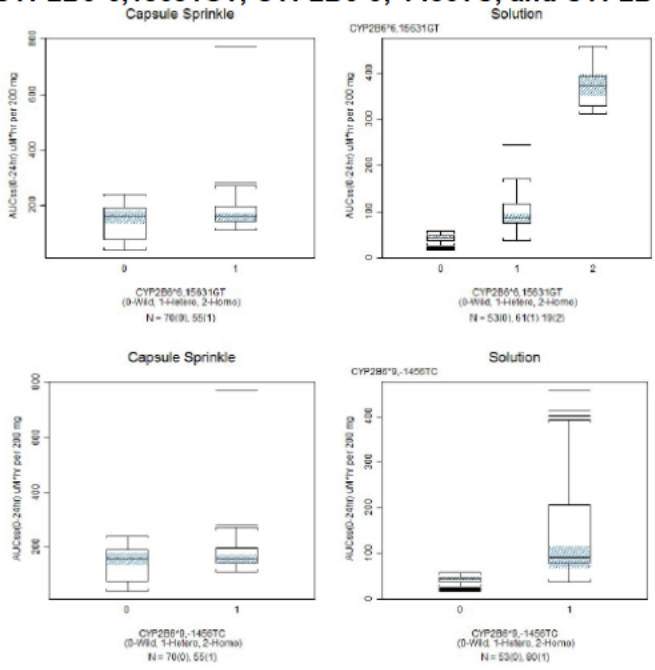
Based on the weight range of pediatrics included in the study (lowest body weight of 3.3 kg), concerns regarding the volume of administration, the increase in mg/kg dosing in pediatrics <3.5 kg, and that the 5th percentile body weight for a 3 month old pediatric subject (US CDC growth charts, female) is 4.5 kg, the review team decided to reduce the minimum weight to 3.5 kg. This restriction in body weight is not anticipated to impact drug availability and dosing options for pediatrics and is intended to avoid dosing recommendations that may imply treatment is permissible in pediatrics <3 months of age.

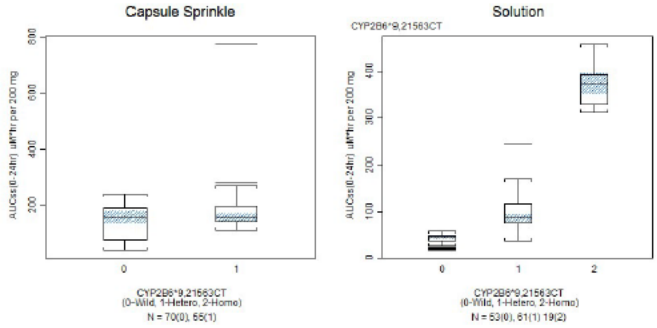
3.2.3.4 Ad-hoc Evaluation of Pharmacogenomic Data

The final PK model with the updated dataset was used for the exploratory evaluation of pharmacogenomics information. Due to the limited data availability (28 subjects from AI266922 only), this evaluation was performed in an ad-hoc fashion, and 1 SNP at a time was tested. The pharmacogenomics information as covariates was added onto clearance in the final model and the parameters were re-estimated.

In this analysis, CYP2B6*6,15631GT, CYP2B6*9,21563CT, and CYP2B6*9,-1456TC showed a significant impact on efavirenz clearance while MDR-1 rs2235040, CYP3A5*6, and CYP2B6 18273GA did not. These results were similar to the previous analysis[1]. Figure 12 visualize the effect of genetic polymorphism for gene on the exposure of efavirenz. Prediction was performed using a sampling scheme of 0, 1, 2, 4, 6, 8, 12, and 24 hours post actual dose for the subjects with pharmacogenomics information. Patients had multiple PK visits, and every PK visit was used for this AUC prediction. Thus, numbers of AUCs in these plots are greater than the number subjects.

Figure 12: Predicted Dose Normalized AUCss vs. Pharmacogenomic Polymorphism - CYP2B6*6,15631GT, CYP2B6*9,-1456TC, and CYP2B6*9,21563CT





Source: Sponsor's population PK report, pg 89-91
*Reviewer's comment: The number of additional subjects with CYP2B6 genotype data from AI266922 was small (n=28; 14 subjects with G/G genotype, 13 subjects with G/T genotype and 1 subject with T/T genotype) and hinders interpretation of these observations. However, a general trend of higher efavirenz exposure was seen in subjects with a CYP2B6 516 G>T substitution (i.e. G/T at CYP2B6 position 516 compared to subjects with G/G; (CYP2B6*6POS+15631). This is in agreement with published literature results the report 3-fold decrease in efavirenz clearance in adults homozygous for the 516G>T substitution (TT) and a 1.4-fold decrease in efavirenz clearance for adult subjects heterozygous for the substitution (GT)[2]. It is also in agreement with published pediatric data that reported a 1.8-fold and 1.3-fold decrease in efavirenz clearance for pediatric subjects homozygous (TT) and heterozygous (GT) for the substitution compared to wild type (GG)[3]. An impact of higher exposure on common efavirenz safety signals (rash, liver toxicity, psychiatric, etc.) could not be identified from the available data. In addition, there were multiple pediatric subjects doses at >2-fold the proposed dosing, with observed exposures similar to those predicted to result in poor metabolizers, however, no relationship between efavirenz exposures and safety signals could be identified in this data. There were two separate publications documenting the potential for efavirenz involvement in Torsades de Points[4], and greater QT prolongation in poor metabolizers compared to regular metabolizers[5]. The impact of these observations remains to be evaluated as no exposure data was provided for the above published efavirenz QT analysis and no thorough QT study for efavirenz was previously performed.*

1) Report on the associations between genetic polymorphism of CYP2B6, CYP3A4/5, and MDR-1 genes and the pharmacokinetics of efavirenz. Bristol-Myers Squibb Research and Development; 2006. Document Control No. 930018246. [Submitted November 5, 2009]

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

3) Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. J Acquir Immune Defic Syndr 2007;45(3):280-285.

4) Castillo R, Pedalino RP, El-Sherif N, et al. Efavirenz-associated QT prolongation and Torsade de Pointes Arrhythmia. Ann Pharmacother 2002; 36: 1006-8.

*5) Abdelhady A, Thong N, Kreutz Y, et al. Association of the CYP2B6*6 allelle with efavirenz-induced QT interval changes at steady state in healthy volunteers. Poster presented at ASCPT 2013, Indianapolis, IN.*

3.2.4 Summary of Subjects with Efavirenz PK Data for the Exclusivity Summary

During the course of the efavirenz review, a question was raised regarding the number of pediatric subjects in each age group for which PK data was available. The pediatric Written Request required that the sponsor include 6 subjects 3 to <6 months, 6 subjects 6 to <2 years, 12 subjects 2 years to <6 years, 8 subjects 6 to <12 years, and 6 subjects 12 to 16 years. This Written Request was issued prior to when data from PACTG 382 Cohort 1 was originally provided; as such, data from those subjects that had already been submitted as part of the original NDA in June 1998 could not be used to fulfill the efavirenz Written Request. The review team performed a summary count of subjects from PACTG 1021, and

AI266922 with one or more efavirenz concentration sample available. The summary count of the subjects by study is presented below in Table 11 and demonstrates that there are sufficient numbers of pediatric subjects in all age groups from studies PACTG1021 and AI266922 to fulfill the Written Request.

Table 11: Summary of Pediatric Subjects by Study and Age Group with One or More Efavirenz PK Sample Available

	PACTG 382 (N)	PACTG 1021 (N)	AI266922 (N)	Total (N)	Total (1021, 922) (N)	Requested
>=3 to <6 months	0	1	8	9	9	6
>= 6 months to <2 years	0	2	14	16	16	6
>= 2 years to <6 years	16	6	8	30	14	12
>=6 years to <12 years	48	14	0	62	14	8
>=12 years to <17 years	11	8	0	19	8	6

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

/s/

VIKRAM ARYA
04/08/2013

JEFFRY FLORIAN
04/08/2013

ISLAM R YOUNIS
04/08/2013