EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2015
EMA/260283/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sustiva

International non-proprietary name: EFAVIRENZ

Procedure No. EMEA/H/C/000249/II/0126/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ARV	Anti-retroviral
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-T)}$	AUC from zero to the last quantifiable time point
$AUC_{(INF)}$	AUC from zero to infinity
$AUC_{(TAU)}$	EFV area under the plasma concentration-time curve for 1 dosing interval
$AUCss_{(0-24)}$	Area under the concentration-time curve in 24 hours at steady state
C_0	Pre-dose Concentration at steady state
CARES	Corporate Adverse Event Reporting System
CHMP	Committee for Medicinal Products for Human Use
CI(s)	Confidence Interval(s)
CL/F	Oral Clearance
Cl/F/kg	Oral clearance per kg of body weight
Cmax	Maximum plasma Concentration
CNS	Central Nervous System
CVR	Confirmed Virologic Response
CYP	Cytochrome P450
DdI	Didanosine
DHCP	Direct Healthcare Professional Communication
DILI	Drug Induced Liver Injury
EFV	Efavirenz
Fpen	Penetration Factor
FTC	Emtricitabine
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practices
HAART	Highly Active Antiretroviral Therapy
HIV-1	Human Immunodeficiency Virus type-1
HPCL	High-performance liquid chromatography
LC	Liquid Chromatography
LEAP	Liquid Expanded Access Program
LLQ	Lower Limits of Quantification
MAA	Marketing Authorization Application
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary of Regulatory Activities
MS	Mass Spectrometry
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NPP	Oral Liquid Named-Patient Programs
NRTI	Nucleoside Reverse Transcriptase Inhibitor
pcVPC	Corrected Visual Predictive Check
PD	Pharmacodynamics
PEC	Predicted Environmental Concentration

PECsw	Predicted Environmental Concentration in surface water
PK	Pharmacokinetics
PL	Package Leaflet
PNEC	Predictive No effect Concentration
PPK	Population Pharmacokinetics
QD	Quaque Die (once daily)
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SNP(s)	Single Nucleotide Polymorphisms
SOC	System Organ Class
TB	Tuberculosis
VR-OC	Virologic Response-Observed Cases
WAM	Wald's approximation method

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 17 January 2014 an application for a group of variations.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Sustiva	EFAVIRENZ

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.7.a	C.I.7.a - Deletion of - a pharmaceutical form	Type IB	I, IIIA, IIIB and A

Extension of indication for the treatment of HIV-1 to include children from 3 months to 3 year of age and weighing at least 3.5kg and removal of the oral solution pharmaceutical form for Sustiva (efavirenz). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.6 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly. In addition, the SmPC, Labelling and Package Leaflet of the oral solution were proposed to be deleted.

The group of variations proposed amendments to the Annex A, Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Filip Josephson

Timetable	Dates
Submission date	17 January 2014
Start of procedure:	21 February 2014
CHMP Rapporteur Assessment Report	24 April 2014
PRAC Rapporteur Assessment Report	30 May 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	08 May 2014
CHMP comments	12 May 2014
Rapporteur Revised Assessment Report	20 May 2014
Request for supplementary information (RSI)	22 May 2014
CHMP Rapporteur Assessment Report	06 October 2014
CHMP comments	13 October 2014
Rapporteur Revised Assessment Report	21 October 2014
Request for supplementary information (RSI)	23 October 2014
PRAC Rapporteur Assessment Report	26 January 2015
CHMP Rapporteur Assessment Report	02 February 2015
PRAC Rapporteur Updated Assessment Report	04 February 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 February 2015
Opinion	26 February 2015

2. Scientific discussion

2.1. Introduction

Sustiva (efavirenz; EFV) is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) that is used in the treatment of Human Immunodeficiency Virus type-1 (HIV-1) infection, and is authorised for use in combination with other antiretroviral agents as part of the Highly Active Antiretroviral Therapy (HAART). The recommended adult dose for EFV is 600 mg once daily (QD).

Sustiva is currently indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children 3 years of age and older with a recommended dose based on body weight that ranges from 200mg QD for children weighing 13 to < 15 Kg up to 600 mg QD for children weighing at least 40 Kg. The following pharmaceutical forms are authorised to cover the different weight bands: 50 mg, 100 mg and 200 mg hard capsules, 600 mg film-coated tablets and 30 mg/ml oral solution.

Efavirenz, in combination with 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs), is the preferred NNRTI for initial therapy of children ≥3 years of age based on clinical trial experience in children (oral solution and capsule sprinkle), efavirenz is not authorised for use in children <3 years of age in the European Union, while it is authorised for use in children at least 3 months of age weighing at least 3.5 kg in the United States.

This grouped variation application was submitted with the purpose to extend the indication for Sustiva to include children from 3 months of age to less than 3 years of age and weighting at least 3.5 kg.

In addition, the MAH proposed an upgrade to the already authorised “capsule sprinkle” dosing method as primary means of dosing for young patients and those who cannot swallow capsules and/or tablets and as a consequence the removal of the oral solution pharmaceutical form for Sustiva.

The capsule-sprinkle dosing method has been already authorised as alternative dosing method (EMEA/H/C/00249/II/0079) as is currently in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) for children older than 3 years. The MAH considered less confusing for caregivers to have a single dosing method for all children older than 3 months who cannot swallow intact capsules rather than maintaining the availability of the oral solution only for children between the ages of 3 and 6 years (the approximate age at which children can reliably swallow capsules).

2.2. Non-clinical aspects

The entire battery test required for non-clinical studies were evaluated during the initial marketing authorisation application. No new clinical data have been submitted in support of this extension of indication, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided the results of the previously authorised medicinal product Atripla (EMEA/H/C/000797), a fixed dose combination of efavirenz, tenofovir and emtricitabine, sufficiently as no significant environmental exposure is expected to occur as results of this extension of indication.

In the Marketing Authorization Application (MAA) of Atripla, the Predicted Environmental Concentration in surface water (PECsw) of efavirenz was determined to be 6.9x10-5 µg/L.

Additional data provided during the assessment

During the evaluation the MAH was requested to demonstrate that no significant increase in environment was expected to occur focusing on the new Predicted Environmental Concentration (PEC) value.

The MAH refined the market Penetration Factor (Fpen) to account for the new patient population included in this extension of indication in accordance with the Q&A document on the "Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010). The data provided is shown below:

$$Fpen\text{-}refined = (CONai)/(DOSEai * n_{i,\ region} * N_d)$$

Fpen	Market Penetration	-----
CONai	periodical consumption of active ingredient in a particular region per year (2014 projected consumption in the EU)	17,635,000,000 mg
DOSEai	maximum daily dose consumed per inhabitant	600 mg/(inh-d)
$n_{i,\ region}$	number of inhabitants in a particular region (EU population in 2013 from Eurostat)	505665739
N_d	number of days per year	365 days

$$Fpen\text{-}refined = (17,635,000,000)/(600 * 505665739 * 365)$$

$$Fpen\text{-}refined = .00016.$$

Using the Fpen-refined, the PECsw was recalculated as shown in the following equation:

$$PEC_{SW} = (DOSEai * Fpen)/(WASTEWinhab * DILUTION)$$

PEC_{SW}	Predicted environmental concentration in surface water	-----
DOSEai	maximum daily dose consumed per inhabitant	600 mg/(inh-d)
Fpen	market penetration	0.00016
WASTEWinhab	amount of wastewater per inhabitant per day	200 L/(inh-d)
DILUTION	dilution factor	10 (Default)

$$PEC_{SW} = (600 * 0.00016)/(200 * 10)$$

$$PEC_{SW} = 4.8 \times 10^{-5}$$

The newly calculated PECsw was lower than the value in the Atripla MAA (6.9x10-5 µg/L) and below the regulatory threshold of 0.01 µg/L set out in the guideline on the "Environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 21*).

Since the expanded new paediatric population is very limited in patient numbers and is a subset of the population already included in the environmental risk assessment of Atripla (EMEA/H/C/000797) and Sustiva (EMEA/H/C000249), it was concluded that no significant increase in environmental exposure is expected to occur following this extension of indication.

2.2.2. Discussion and conclusion on non-clinical aspects

A conservative estimate of the PEC in sediment which assumed no metabolism, no removal/degradation in the wastewater treatment plant/receiving waters, and worst case partitioning from water to sediments was performed. The PEC/Predictive No effect Concentration (PNEC) ratio was significantly less than 1, indicating that efavirenz is unlikely to represent a risk to the sediment environment. The justification provided by the MAH was considered acceptable by the CHMP.

The CHMP agreed that no increase in the environmental exposure is expected and that efavirenz does not constitute a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practices (GCP)

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Summary of main studies

Three main paediatric studies have been submitted in support of this application (Studies PACTG 382, PACTG 1021 and AI266922)

Across these studies, 182 subjects between the ages of 3 months and 21 years were treated with efavirenz. Of these subjects, 90 received at least 1 dose of the EFV oral solution and 130 received at least 1 dose of the EFV capsules, including 41 subjects who received both formulations.

Study PACTG 382: This was a Phase 1/2 open-label study that evaluated efavirenz in combination with nelfinavir (NFV) and NRTIs in ARV-naive or -experienced HIV-infected children 3 months to 16 years of age. This study was conducted from November 1997 to January 2007.

Study PACTG 1021: This was a Phase 1/2 open-label study that evaluated the oral solution of EFV in combination with emtricitabine (FTC) and didanosine (ddI) in ARV-naïve (or very limited ARV exposed) HIV-infected subjects from 90 days to 21 years of age. This study was conducted from September 2001 to January 2009.

Study AI266922: This was a Phase 2 open-label study evaluating EFV (in oral solution and capsule sprinkle formulation) administered in combination with ddI and FTC, in ARV-naive or -experienced HIV-infected children 3 months to 6 years of age. This study was conducted from February 2007 through July 2013.

In addition a fourth study, **Study AI266059** was also submitted. This was a bioavailability study conducted in adults and was a Phase 1 open-label, randomized, 3-period, 3-treatment crossover study balanced for residual effects in 2 treatment groups to assess bioavailability and safety of EFV capsule sprinkle (capsule contents mixed with and administered with a small amount of food or baby formula) relative to the intact capsule formulation administered under fasted conditions.

For completeness the MAH submitted data of the **Liquid Expanded Access Program (LEAP) / Oral Liquid Named-Patient Programs (NPP) studies (programs)** conducted in the paediatric population with the oral solution in countries where this formulation has still not been authorised.

Based on available Pharmacokinetics (PK) data from paediatric Studies PACTG 382, PACTG 1021, and Study AI266922, and the adult relative bioavailability study, Study AI266059, a Population Pharmacokinetics (PPK) model was developed to characterise EFV PK in paediatric subjects (Study no. 930057409).

Furthermore, the PPK model was used to simulate and optimise the recommended dose for children weighing <10 kg. Criterion used for dose recommendations were EFV area under the concentration-time curve (AUC) levels within the range of 190 to 380 µM.h, which represents the median to 2 x median EFV AUC in adults treated with EFV 600 mg QD, a dose that is known to be efficacious. This was corroborated by the Pharmacodynamics (PD) results of Study PACTG 382 (section 2.3.3).

Finally, data on EFV exposure with regard to Cytochrome P450 (CYP) 2B6 polymorphisms was also provided.

2.3.2. Pharmacokinetics

Methods

The adjusted geometric means, ratios of geometric means, and 90% Confidence Intervals (CIs) of EFV maximum concentration (C_{max}), AUC from zero to the last quantifiable time point ($AUC_{(0-T)}$) and AUC from zero to infinity ($AUC_{(INF)}$) were evaluated.

In some studies, EFV area under the plasma concentration-time curve for 1 dosing interval ($AUC_{(TAU)}$) at steady state and apparent oral clearance per kg of body weight (Cl/F/kg) were also calculated and reported for different age groups and formulations.

The PK parameters were mainly determined using non-compartmental analysis.

In the 3 main studies (Studies PACTG 382, PACTG 1021, and Study AI266922) doses were adjusted based on measured AUCs for each subject. For subjects with AUC values greater than 570 µM (180 mg/L.h), the dose was decreased by 50%. For subjects with AUC values of 380 to 570 µM (120 to 180 mg/L.h), the dose was decreased by 25%. Dose reductions were anticipated for very few subjects. If AUC values were below the threshold set by the protocol (<110 µM or 35 mg/L.h), the contents of a capsule at the same dose (e.g., 390 or 600 mg) were dispersed in a food vehicle (either applesauce, grape jelly or yogurt) rather than attempting further increases in the dose of the solution. The current doses of 390 and 600 mg required administering a volume of 13 to 20 mL given the concentration of 30 mg/mL for the solution and higher doses (volumes) were not practical.

EFV C_{max} and pre-dose concentration at steady state (C_0) or C_{min} for the weight groups <10 kg were compared to those for children with body weights ≥10 to <15 kg using the criteria of median C_{max} and C_0 within 80% to 125% of the reference value. The reference ranges for C_{max} and C_0 were 5.2 to 8.2 µg/mL and 1.9 to 2.9 µg/mL, respectively.

Simulated EFV AUC, C_{max}, and C_0 for subjects who weighed <10 kg were submitted in support of the EFV dosing recommendations.

The PPK analysis (modelling and simulation analysis) utilised PK data collected from the 3 main studies PACTG 382, PACTG 1021, and AI266922 in paediatric HIV patients between 3 months and 21 years of age when treatment began .

Study AI266059 was also included in order to establish bioequivalence between intact capsules and capsule sprinkles with food mix-ins with regard to EFV AUC; thus, capsule and capsule sprinkles were treated as the same formulation throughout the PPK analysis. CHMP considered this acceptable.

The effects of clinically relevant covariates were assessed in the PPK model, including age, weight, gender, race, previous ARV therapy, and co-medication with a Protease Inhibitor.

Analytical methods

The validations performed indicated that the methods fulfilled all requirements regarding linearity, precision, accuracy, sensitivity and specificity. Table 1, provides a summary of the analytical methods used and Lower Limits of Quantification (LLQ) for each study.

Table 1: Summary Information for analytical methods for Efavirenz

Study	Assay method	LLQ (units)
PACTG 382	HPLC	100 ng/mL
PACTG 1021	HPLC	50-90 ng/mL
AI266922	LC/MS/MS	10.0 ng/mL
AI266059	LC/MS/MS	100 ng/mL

LLQ: lower limit of quantification; HPCL: High-performance liquid chromatography; LC: Liquid chromatography and MS: Mass Spectrometry

2.3.2.1. Main paediatric studies:

Study PACTG 382

Title:

"*A phase I/II, 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:

The primary objectives were to study the safety, tolerance and pharmacokinetics of EFV capsules in HIV –infected children who could take the capsule formulation of this medication in a first cohort (Cohort 1). A second cohort (Cohort 2) was accrued to evaluate the safety, PK, immunologic effects and antiviral activity of EFV oral formulation in HIV-infected children, administered with NFV and NRTIs.

Treatment:

The treatment in this study was consistent with mandatory EFV and NFV, combined with a background of at least one NRTI chosen by the investigator.

None of the subjects included in this study was dosed using the sprinkle capsule contents. The dose changes made along the study were based on EFV plasma exposure data.

Dosing regimen:

EFV dosing was based on baseline body weight, but it was adjusted based on subject's body weight at each clinic visit, tolerability, and AUC during treatment. The initial target AUC range for the EFV capsule dose was between 190 to 380 µM•h, which represents the median to 2 x median AUC observed in adults treated with 600 mg EFV QD.

- **Cohort I**: *57 children 3 to 16 years of age* were treated with EFV capsules for 208 weeks. The starting dose was calculated using the equation:

  - *Starting dose = (body weight/70)$^{0.7}$ • 600 mg*

- **Cohort II:** *45 children* were treated with the oral formulation of EFV and were divided into 2 stratas:
    - Stratum 1: children aged ≥ 3 months and < 2 years
    - Stratum 2: children aged ≥ 2 years and ≤ 8 years.

Subjects in Cohort II initially received the 20 mg/mL sugar-containing solution of EFV and later switched to the sugar-free solution (30 mg/mL) or capsules. Total treatment duration was 208 weeks. The starting dose was calculated using the following equation (Algorithm 1):

$$\textit{Initial EFV oral Solution dose} = (\textit{body weight}/70)^{0.7} \bullet \textit{720 mg}$$

A base dose of 720 mg was used in the algorithm for the oral solution due to the approximate 20% reduction in the bioavailability of the EFV oral solution relative to the capsule; 720 mg of the oral solution was expected to provide similar exposures as the 600 mg capsule. Intensive PK samples up to 24 hours post-dose were collected through Week 112 for both Cohorts I and II.

Interim PK results for Cohort II Stratum 1 (≥ 3 months and < 2 years) demonstrated that observed EFV AUCs were lower than the target AUC in the majority of the subjects. Thus, the initial starting dose for paediatric subjects on the EFV oral solution in Cohort II Stratum 1 was revised to 1,200 mg adjusted for body size and resulted in 2 dosing algorithms for subjects in Cohort II Stratum 2. Algorithm 2 was as follows:

$$\text{Initial EFV oral Solution dose} = (\text{body weight}/70)^{0.7} \bullet 1200 \text{ mg}$$

Results and analysis:

Patient disposition

Less than half (46.2%) of the subjects in the relevant age group Cohort II Stratum 1 completed the study protocol, while only 15.4% did so due to clinical endpoints as defined by the protocol. The overall discontinuation rates were very high in the PK study, with overall only 52.9% of subjects at all age groups completed the study protocol. All the younger subjects were treated with the oral solution, with either the former 20 mg/ml formulation or with the commercially available 30mg/ml formulation. Tolerability issues may have contributed to this high discontinuation rates.

Results

Intensive PK evaluations were performed at week 2 and 6. Children with AUC values outside the target range had the doses of EFV and NFV adjusted, and repeated PK evaluations were performed 2 weeks later.

Summary statistics (mean and Standard Deviation (SD)) for EFV PK parameters by cohort, stratum, and formulation at Week 2 in paediatric subjects are provided in Table 2.

Table 2: Study PACTG 382 – Mean (SD) Efavirenz Pharmacokinetic Parameters in Paediatric Subjects

Age Group	Formulation (N)	AUC(TAU) (μM•h)	Cmax (μg/mL)	Cmin (μg/mL)	CLT/F/kg (L/h/kg)
≥ 3 to ≤ 16 years	Capsule (N=49)	242 (186)	4.46 (1.77)	1.93 (1.49)	0.197 (0.084)
≥ 2 to ≤ 8 years	Oral Solution (N=18)	268 (317)	4.64 (4.70)	2.51 (4.16)	1.08 (2.30)
≥ 3 months to < 2 years (Algorithm 1)	Oral Solution (N=9)	221 (228)	4.16 (3.19)	2.01 (3.03)	0.505 (0.323)
≥ 3 months to < 2 years (Algorithm 2)	Oral Solution (N=12)	169 (126)	3.54 (2.92)	1.16 (0.94)	1.09 (1.16)

Algorithm 1: Initial EFV oral solution dose = (body weight/70)$^{0.7}$ • 720 mg.
Algorithm 2: Initial EFV oral solution dose = (body weight/70) $^{0.7}$ •1200 mg.
$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval, CLT/F/kg = body-weight adjusted clearance, C_{max} = maximum concentration, C_{min} = minimum concentration, and SD = standard deviation

At Week 2, children ≤2 year of age received higher median solution dose (31.3 mg/kg) compared to children >2-5 years (16.3 mg/kg) or >5-12 years (14.3 mg/kg) of age. A similar age related trend was also observed for the capsule formulation, where the median dose for children >2-5 years of age was 13.2 mg/kg compared to a median dose of 8.8 mg/kg for children >12-16 years of age. Irrespective of the formulation used, the dosing records for Week 20 show trends similar to those noted at Week 2. This dose distribution is explained by the fact that greater clearance in younger children necessitated the use of higher doses to attain AUC within the target range.

In children ≥3 years of age treated with EFV capsules at a dose of 600 mg adjusted for body weight, EFV exposures (C_{max}, AUC, and C_{min}) were comparable to those observed in adults treated with 600 mg QD.

Of the 18 children ≥2 to ≤8 years of age treated with the oral solution at a dose projected to provide an equivalent dose of 600 mg adjusted for body weight, 11 had an EFV AUC below the protocol-defined target range, while 3 subjects had an EFV AUC above the target range. CLT/F/kg of EFV was higher after treatment with the oral solution relative to the capsule.

Although not apparent by the mean values displayed in Table 2, after treatment with the oral solution, median EFV CLT/F/kg was higher in subjects <2 years of age (0.510 L/h/kg and 0.745 L/h/kg for Algorithms 1 and 2, respectively) relative to subjects 2 years of age and older (0.350 L/h/kg).

This was consistent with the negative correlation (r^2= 0.20; P< 0.0001) between Oral Clearance (CL/F) and age. Further comparison showed that CL/F for the > 2-5 year and > 5-12 year age groups in Cohort II was approximately 32% and 57% higher, respectively, than CL/F for the same age groups in Cohort I; and CL/F for the ≤2 year age group (Cohort II) was approximately 121-248% higher than the CL/F for the other age groups in Cohort I and II. Differences in bioavailability between the two formulations (20% higher for the capsule formulation) may have contributed to this discrepancy; however, differences in age between the two cohorts seem to be the primary reason.

Conclusions from PK analysis:

It was concluded that an apparent oral clearance of EFV in younger children> 3 months to ≤2 years of age was greater than that in older children. As a result, higher doses are needed for younger children ≤2 years of age in order to attain EFV exposures similar to those achieved in older children and adults. The negative correlation between CL/F and age was expected.

None of the subjects included in this study was dosed using the sprinkle capsule contents, therefore no relevant information regarding the use of the sprinkled capsule contents may be derived from this study in the target age range.

Additional data provided during the assessment

During the evaluation the CHMP identified the following concerns and clarifications were requested:

1. The differences of the mean values for the PK parameters (AUC, C_{max} and C_{min}) and mean Cl/F/Kg for the same age group (≥3 months to <2 years) between the initial oral solution dose when calculated using Algorithm 2 (1,200 mg adjusted for body size) and to Algorithm 1 (720 mg adjusted for body size). It was lower when using algorithm 2 relative to algorithm 1 (Table 2)
2. The lack of presentation or discussion of plausible explanations for the age related differences in clearance excluding a differences in bioavailability between the two formulations (oral and capsules).

Concern 1:

The MAH provided a summary statistics for EFV C_{max}, $AUC_{(TAU)}$and C_{min} for subjects dosed using Algorithm 1 or 2 (Table 3) and a scatter plot depicting individual EFV $AUC_{(TAU)}$values at Week 2 for Cohort II-Stratum 1 (subjects receiving oral solution by different algorithms) (Figure 1). The mean values of the PK parameters for the subjects in Cohort II-Stratum 1 dosed by Algorithm 2 (base dose of 1,200 mg EFV) were all lower than Algorithm 1 (base dose of 720 mg). The apparently aberrant finding for the mean values of C_{max}, $AUC_{(TAU)}$ and C_{min} was due to the small number of subjects, and 1 subject in particular, whose EFV $AUC_{(TAU)}$was very high relative to the other subjects after being dosed according to Algorithm 1. See Figure 1, where this subject appears as an outlier at an EFV $AUC_{(TAU)}$ of 755 uM*h. This subject had a CYP2B6-516T/T genotype that likely contributed to the observed higher EFV systemic exposure (and lower EFV CL/F relative to the other subjects. The CYP2B6 516 G<T substitution on *6 haplotype has a considerable effect on EFV systemic exposure. Based on the literature, the median $AUC_{(TAU)}$ of EFV is approximately 3-fold higher in CYP2B6 516T/T homozygotes as compared to G/G homozygotes, and is intermediate in G/T heterozygous individuals, this explained the higher exposure in that particular subject.

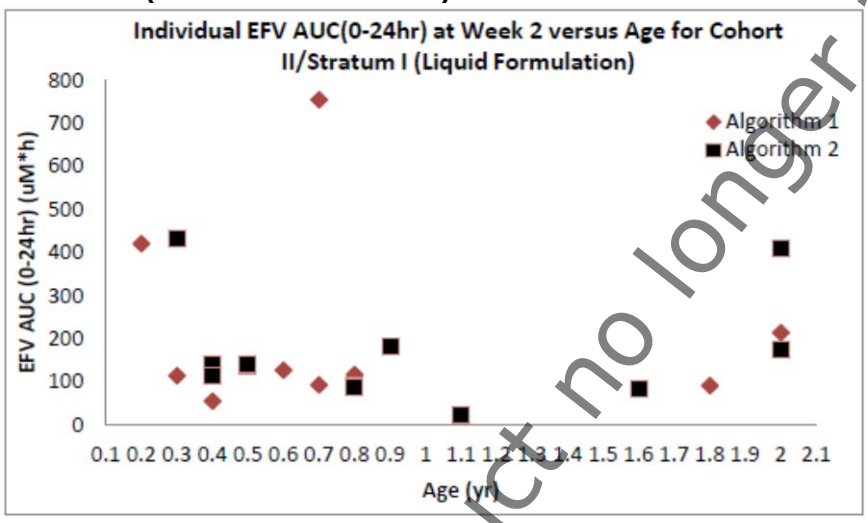
Summary statistics for EFV observed PK parameters excluding this outlier was also provided by the MAH and are shown in Table 4. This was conducted as a post-hoc analysis. The data showed that the range between the 2 groups was comparable. There was another subject in this group (Algorithm 1) with a TT homozygote, where the $AUC_{(TAU)}$ was 421 μM•h, a value slightly beyond the target range. This subject also contributed to higher mean PK values for the Algorithm 1 subjects relative to those in Algorithm 2, especially since no Algorithm 2 subjects had CYP2B6 516T/T homozygotes.

Table 3: Summary Statistics for Efavirenz Pharmacokinetic Parameters for Subjects in Cohort II-Stratum 1 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
$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval; C_{max} = maximum concentration, C_{min} = minimum concentration; Geo Mean = Geometric Mean.

Figure 1: Scatter Plot of Efavirenz $AUC_{(TAU)}$ at Week 2 versus Age for Subjects in Cohort II - Stratum 1 (Solution Formulation)



$AUC_{(0-24)}$ = area under the plasma concentration – time curve from 0-24 h

Table 4: Summary Statistics for EFV Pharmacokinetic Parameters for Subjects in Cohort II-Stratum 1 That Received the Oral Solution at a Dose Based on Algorithm 1 and Algorithm 2 (Excluding the Outlier Subject)

Algorithm (N)	Cmax (µg/mL)	AUC(TAU) (µM*h)	Cmin (µg/mL)
1[8]			
Geo. Mean (%CV)	2.92 (56)	128 (76)	0.68 (118)
Median (min,max)	2.61 (1.58-7.20)	116 (55 - 421)	0.75 (0.12 - 4.10)
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
$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval; C_{max} = maximum concentration, C_{min} = minimum concentration; Geo Mean = Geometric Mean.

Furthermore, the MAH claimed that dosing EFV by solution is likely to be highly variable in subjects ≥ 3 months to < 2 years of age. Although there was a small reported number (n=1, 4%) of cases of vomiting and spitting, the high variability in PK parameters for both groups could be attributed, at least in part, to issues associated with dosing liquids in this age group, individual variability in absorption, and overall poor bioavailability of the oral solution.

Although there was a ~2-fold difference in mean CL/F/kg for the same age group using Algorithm 1 and Algorithm 2 (0.505 and 1.09L/h/kg, respectively), the difference in CL/F/kg using the median values was only 0.51 and 0.745L/h/kg, respectively. The CHMP considered this clarification satisfactory.

Concern 2:

The MAH initially stated that the higher Cl/F/kg values obtained in younger children were not mainly attributable to a lower bioavailability of the oral solution but to the differences in age between the cohorts (the mean Week 2 AUC in Cohort II – oral solution – appeared to be lower than that in Cohort I – capsule).

The MAH suggested pharmacogenomics as a possible reason for the observed apparent age-related differences. The difference in the CL/F between cohort I (capsule) and cohort II (oral solution) groups was attributed to an outlier in the oral solution group that was included in the summary statistics of the mean EFV systemic exposures between the solution and capsule for subjects < 8 years of age. In Cohort II, none of the 18 subjects were < 3 years of age. Similarly, in Cohort I, all subjects enrolled were > 3 years and < 8 years of age. Subjects receiving the EFV oral solution had somewhat higher exposure $AUC_{(TAU)}$ relative to adults treated with the EFV capsules. The mean PK values for the 2 groups were generally similar, except for CL/F that had lower values in the capsule-treated subjects. This is shown in Table 5.

The difference in the CL/F between these groups was attributed to an outlier in the oral solution group that was included in the summary statistics. The same summary statistics (EFV PK statistics at Week 2) were provided excluding the outlier and are presented in Table 6. These results presented a more comparable mean EFV CL/F values between the 2 groups (0.32 ± 0.13 and 0.21 ± 0.08 L/h/kg for oral solution and capsule, respectively). In this case, genotypic information could not be correlated with exposure.

Table 5: Efavirenz Pharmacokinetic Parameters in HIV-infected Paediatric Subjects 8 Years of Age and Younger in Cohort I (Capsules) and Cohort II-Stratum 2 (Oral Solution)

PK Parameters Mean (SD)	Cohort II-Stratum 2 Children: Oral Solution (N=18)	Cohort I Children: Capsule (N=29)
Cmax (µM)	14.7 (14.9)	15.1 (5.8)
Cmin (µM)	8.0 (13.2)	5.2 (3.4)
AUC(TAU) (µM*h)	268 (317)	216 (91)
CLT/F (L/h/kg)	1.08 (2.3)	0.21 (0.08)

$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval, CLT/F/kg = body-weight adjusted clearance, C_{max} = maximum concentration, C_{min} = minimum concentration, SD = standard deviation and PK= Pharmacokinetics.

Table 6: Efavirenz Pharmacokinetic Parameters and Statistical Summary for Week 2 in Patients 8 Years and Younger - Cohort II-Stratum 2 Suspension and Cohort I Capsule (Excluding Outlier)

PK Parameters Mean (SD)	Cohort II-Stratum 2 Children: Oral Solution (N=17)a	Cohort I Children: Capsule (N=29)
Dose (mg)	386 (168)	378 (140)
Cmax (µM)	11.84 (5.37)	15.1 (5.8)
Cmin (µM)	5.20 (4.24)	5.2 (3.4)
AUC(TAU) (µM*h)	188.3 (104.0)	216 (91)
CLT/F (L/h/kg)	0.32 (0.13)	0.21 (0.08)

$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval, CLT/F/kg = body-weight adjusted clearance, C_{max} = maximum concentration, C_{min} = minimum concentration, SD = standard deviation and PK= Pharmacokinetics.

Another possible reason suggested by the MAH for this difference was the fact that a body weight-corrected clearance is usually higher in younger subjects as compared to older subjects.

The CHMP considered this clarification satisfactory.

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 naive or very limited antiretroviral exposed paediatric subjects*".

Objectives:

Primary Objectives:

• To determine the long-term safety and tolerance of a regimen of FTC + EFV + ddI administered once daily in HIV-infected paediatric subjects who are naïve, or have very limited exposure, to 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, paediatric subjects.

Secondary Objectives

• To determine EFV systemic exposure following administration of the currently recommended paediatric 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.

Treatment:

Forty-three children participated in this study, including 6 children 3 months to < 3 years of age (Group 1), 21 children 3 to 12 years of age (Group 2), and 16 children 13 to 21 years of age (Group 3). Subjects in Group 1 were dosed for 96 weeks and subjects in Groups 2 and 3 were dosed for 192 weeks.

The regimen was to be based on once daily triple combination of:

1) FTC administered at 6 mg/kg up to 200 mg/day.

2) ddI administered at 240 mg/m^2 up to a daily maximum of 400 mg.

3) EFV was available as a 30-mg/mL sugar-free oral solution and 50-, 100-, or 200-mg capsules. EFV was administered QD in the evening (Groups 2 and 3) or in the morning (Group 1 for 12 weeks) with FTC and ddI.

Dosing regimen:

Group 1 subjects weighing < 10 kg were given 390 mg QD EFV and subjects weighing 10 to 32.5 kg were given 600 mg QD EFV. Groups 2 and 3 subjects were given up to a maximum of 600 mg QD capsules or 720 mg EFV oral solution (dose based on body weight). Subjects in Group 1 were dosed for 96 weeks and subjects in Groups 2 and 3 were dosed for 192 weeks. During the trial it was allowed to switch from oral solution to the capsule sprinkled for dose adjustment purposes. This was the case for subjects in Group 1 who had an AUC below the threshold value, EFV capsule sprinkles were administered.

Doses were scaled for the children less than 2 years of age using a reference dose of 1200 mg (approximately twice the currently used adult dose) and the median AUC remained considerably lower than the average value for adults.

Dose selection for age group 1 for Study P1021 was consistent with dose scaling used for Study PACTG 382 using a reference dose of 2000 mg (67% increase from dose used for children less than 2 years in Study PACTG 382) and the CL/F data from older children receiving EFV oral solution in Study P1021. As the anticipated weight range was relatively modest and there was considerable variability in CL/F not explained by body weight, the dose selected for children less than 3 years was 390 mg for children less than 10 kg and 600 mg for children from 10 to 17 kg.

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. 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.

Results and analysis:

Patient disposition

The discontinuation rates were considerably low but still very high in the target age group 1, aged between 3 months to 3 years in which only 2/6 subjects completed the study. The available information indicated that these subjects may have only been treated with the oral solution at 30 mg/ml.

Results

Despite being one of the objectives in Study protocol PACTG 1021, only one subject was dosed with the sprinkled capsule contents. PK samples were collected up to 24 hours post-dose at Week 2 and Week 12. Additional intensive sampling was collected following dose modifications or formulation changes. Table 7 describes the summary statistics for EFV PK parameters at the initial dose and formulation.

Table 7: Study PACTG 1021 – Mean (SD) Efavirenz Pharmacokinetic Parameters at the Initial Dose

Age Group	Formulation	AUC(TAU) (μM•h)	Cmax (μg/mL)	Cmin (μg/mL)	CLT/F/kg (L/h/kg)
1 (≥ 3 months to < 3 years)	Oral Solution (N=6)	295 (281)	5.08 (3.50)	2.83 (3.47)	1.04 (0.99)
2 (≥ 3 to < 13 years)	Oral Solution (N=12)	160 (53.0)	3.52 (1.27)	1.42 (0.61)	0.40 (0.19)
	Capsule (N=6)	227 (68.6)	4.69 (1.14)	2.29 (1.19)	0.19 (0.079)
3 (≥ 13 to < 22 years)	Capsule (N=15)	258 (79.0)	5.57 (1.15)	2.58 (1.06)	0.12 (0.037)

$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval; CLT/F/kg = body-weight adjusted clearance; C_{max} = maximum concentration; C_{min} = minimum concentration and SD = standard deviation

EFV clearance appears to be highest in children <3 years of age treated with the oral solution. In subjects 3 to 13 years of age (Group 2), EFV CLT/F/kg was higher in those subjects treated with the oral solution relative to the capsule. In subjects 13 to 22 years of age (Group 3), EFV exposures were largely similar, if not somewhat higher, than historical data in adults treated with the same dose of EFV.

Conclusions from PK analysis

The study results are in agreement with the Study PACTG382 regarding the relation between EFV CL/F and children age. Again, EFV CL/F in younger children >3 months to ≤3 years of age is much greater than in older children (3 to 12 years of age and 13 to 21 years of age). Therefore, higher doses are required for younger children ≤3 years of age in order to achieve EFV exposures similar to those achieved in older children and adults.

Both studies (PACTG 382 and PACTG 1021) suggested that the PK of EFV is age-dependent.

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 characterise the PK properties of EFV in oral solution formulation and capsule formulation administered as a sprinkle preparation in infants and children 3 months to 6 years of age.

Secondary objectives

- To evaluate the antiviral effect of regimens consisting of EFV, ddI and FTC, as measured by the proportion of subjects with plasma HIV RNA levels < 400 copies/mL and < 50 copies/mL at 24 and 48 weeks, respectively.
- To assess antiviral activity through 24 weeks, 48 weeks and/or at completion of study, based on HIV RNA change from baseline.
- To assess the safety and tolerability of EFV-based therapy in a paediatric population.
- To assess change in CD4 count and CD4 percentage from baseline through 24 weeks, 48 weeks and/or at completion of study.
- To characterise the PK profile of ddI when administered as a single daily dose in children.
- To assess the relationship between EFV PK parameters and antiviral effects.
- To assess the resistance profile in subjects failing an EFV solution-containing regimen.
- To explore the relationship between EFV PK parameters and polymorphism of CYP2B6, CYP3A4, CYP3A5 and p-glycoprotein.

Treatment

There were 4 treatment groups:

Group 1 included 12 infants 3 months to <6 months of age,
Group 2 included 10 infants/children 6 months to <2 years of age,
Group 3 included 4 children 2 to <3 years of age,
Group 4 included 6 children 3 to 6 years of age.

The treatment is this study consisted of:

1) ddI (paediatric powder for oral solution or capsules of enteric-coated beads): 240 mg/m^2 QD; maximum daily dose of 400 mg.

2) FTC oral solution 6 mg/kg QD; maximum daily dose of 240 mg.

3) EFV: All subjects enrolled were initially treated with EFV oral solution however twelve subjects enrolled after protocol amendment were initially treated with EFV capsule (11 in Group 1 and 1 in Group 3).

Dosing regimen

The EFV formulation and/or dose was individually adjusted in subjects, if their EFV $AUC_{(TAU)}$ fell outside the protocol-defined target range of 110 to 380 µM•h (approximate 10^{th} and 90^{th} percentiles for adult exposure when EFV capsule formulation is dosed as 600 mg/day).

Subjects in Groups 1, 2, and 3 received EFV oral solution at the start of the study (390 mg for children weighing <10 kg and 600 mg for children weighing 10 to 17 kg) and were switched to capsule sprinkle if their EFV $AUC_{(TAU)}$ was below the target range (110 µM•h) or not able to tolerate the oral solution. After protocol amendment, all new subjects started treatment with the EFV capsule sprinkle formulation and the dosing nomogram used to estimate starting doses was modified so that a relatively reduced dose of capsule sprinkle was used.

Children in Group 4 received an EFV oral solution up to a maximum dose of 720 mg (dose based on body weight).

Subjects in Groups 1 and 2 that initiated the study with the capsule sprinkle were treated with 300 mg if their body weight was <10 kg and 400 mg for body weight ≥10 to ≤17 kg. The capsule sprinkle dosing nomogram for Group 3 was not altered. This altered dosing nomogram for initiation of the study with the capsule sprinkle only impacted subjects that enrolled in Group 1, as Group 2 had filled prior to the modification.

Efavirenz was administered in accordance with weight-based dosing nomograms, and included 1 of the following preparations in a QD dose:

- EFV capsules (50 or 200 mg),
- EFV capsule (50 or 200 mg) mixed with formula or a small amount of caregiver-selected food vehicle (e.g., yogurt, applesauce, or grape jelly),
- EFV oral solution (30 mg/mL).

Results and analysis

Patient disposition

The overall discontinuation rates were very high, only 45.9% of the subjects completed participation in the study. The age group with a higher overall discontinuation rate was the younger age Group 1, even though a significant number of subjects in this group may have been administered the sprinkled capsule contents from the study outset.

Results

Only 24 subjects in Study AI266922 were treated with the sprinkled capsule contents in Study AI266922 (14, 7, and 3 in Groups 1, 2, and 3, respectively). Of these, only 12 (11 in Group 1 and 1 in Group 3) were initially treated with the sprinkled capsule contents and 12 also received EFV oral solution (3, 7, and 2 in Groups 1, 2, and 3, respectively).

Intensive PK sampling was conducted at Week 2 with samples collected up to 24 hours after the dose. Intensive EFV PK sampling was also conducted at Week 10, if a dose modification or formulation change was necessary based on the Week 2 intensive PK. If additional dose modification was necessary based on the Week 10 intensive PK, intensive PK sampling was conducted at Week 18.

Additionally, EFV trough samples were collected prior to the dose through Week 144. Subjects in Groups 1, 2, or 3 with an EFV AUC below the target range were switched to the EFV capsule sprinkle at a dose of 400 mg for body weight <10 kg and 600 mg for body weight ≥10 to ≤17 kg.

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 at Week 10 intensive PK sample collections was performed. 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).

Summary statistics (mean and SD) for EFV PK parameters by age group and formulation at week 2 are provided in Table 8.

Table 8: Study AI266922 – Mean (SD) Efavirenz Pharmacokinetic Parameters at Week 2 (Initial dose and Formulation)

Age Group	Formulation	AUC(TAU) (µM•h)	Cmax (µg/mL)	Cmin (µg/mL)	CLT/F/kg (L/h/kg)
1 (≥ 3 to < 6 months)	Oral Solution (N=3)	176 (173)	4.52 (3.43)	0.938 (1.33)	2.87 (2.03)
	Capsule (N=9)	428 (289)	11.9 (5.38)	3.32 (3.41)	0.549 (0.401)
2 (≥ 6 months to < 2 years)	Oral Solution (N=10)	84.9 (41.5)	2.29 (1.17)	0.574 (0.329)	3.03 (2.54)
3 (≥ 2 to < 3 years)	Oral Solution (N=3)	109 (74.7)	2.53 (1.72)	0.773 (0.581)	1.59 (0.80)
	Capsule (N=1)	742 (NR)	14.4 (NR)	5.65 (NR)	0.196 (NR)
4 (≥ 3 to < 6 years)	Oral Solution (N=7)	188 (184)	3.71 (3.07)	1.75 (1.94)	0.870 (0.629)

$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval; CLT/F/kg = body-weight adjusted clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; NR = not reported and SD = standard deviation

Conclusions from PK analysis

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 CLT/F/kg appears to be inversely correlated with age in paediatric subjects ≥3 months to ≤ 6 years of age. This is in agreement with the two previously summarised studies (PACTG 382 and PACTG 1021). EFV CL/F in younger children (>3 months to ≤2 years) of age is much greater than in older children (2 to 3 years of age and 3 to 6 years of age).

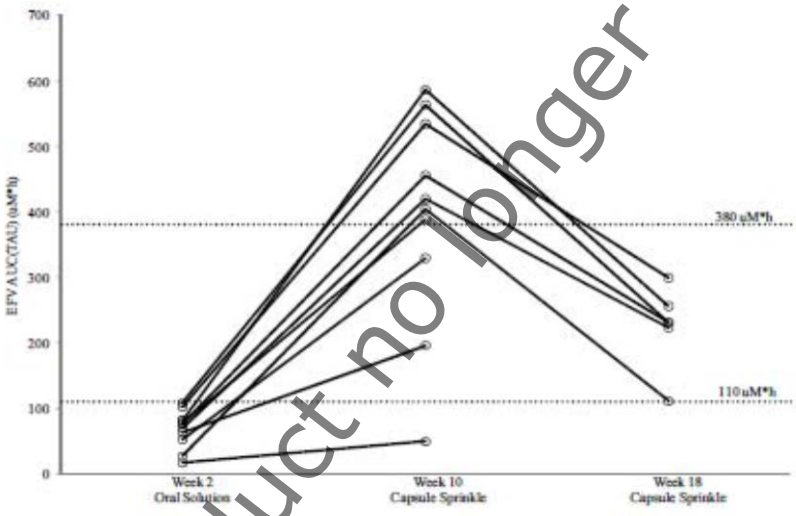
Even though the dose as oral solution was higher (for groups 1, 2 and 3: 390 mg for children weighing <10 kg and 600 mg for children weighing 10 to 17 kg), the capsule sprinkle method of administration in the same age group consistently originated higher values for AUC, C_{max} and C_{min} and obviously a lower clearance (groups 1 and 3). This seemed to reflect differences mostly in the bioavailability of the two formulations and not age-related PK dependence since data from the same age group with different formulations (i.e. group 1, where both oral solution and capsule sprinkle data are available) was compared.

The comparison of PK parameters between different age groups treated with capsule sprinkle is very limited since, with the exception of group 1, only one child (in group 3) was treated with EFV administered by this method.

Additional data provided during the assessment

In this study, subjects < 3 years of age at Week 2 who started on oral solution had suboptimal systemic exposure and they were subsequently switched to the capsule sprinkle (based on the dosing algorithm) at Week 10 that led to higher systemic exposures, the majority of which were higher than the desired upper bound of the target range of 380 µM•h. Consequently, dose reductions, as necessary, were done at Week 18 Figure 2 illustrates that the increase in oral bioavailability from solution to capsule leads to substantially higher EFV systemic exposure.

Figure 2: Scatter Plot of Efavirenz $AUC_{(TAU)}$ for Subjects Less Than 3 Years of Age That Initiated Treatment With the Oral Solution and Required a Switch to the Capsule Sprinkle

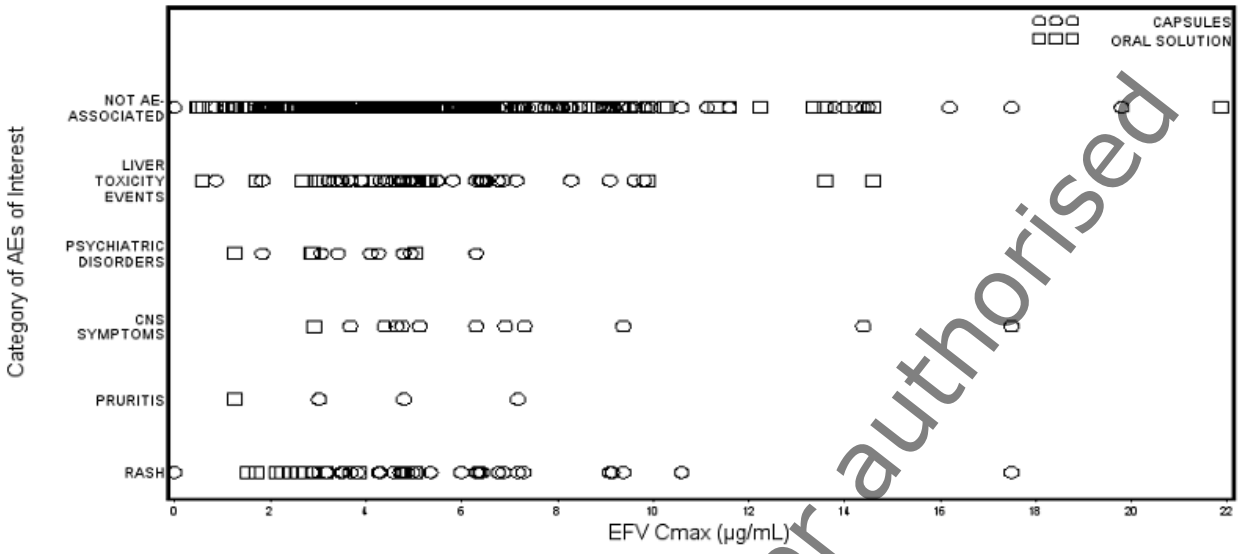


$AUC_{(TAU)}$ = area under the plasma concentration-time curve for 1 dosing interval

The CHMP requested clarification on these results and its potential relation with the occurrence of adverse events. The MAH was also requested to propose caution measures were intended to be implemented to avoid unpredictable EFV exposures when switching young children patients from oral solution to capsule sprinkle dosing method.

The MAH combined the adverse events reported in Studies PCTG 382, PACTG 1021 and AI266922 regardless of investigator-assigned relationship to EFV, and the adverse event s were assessed to determine whether a correlation between EFV C_{max} and an adverse event of interest existed (Figure 3).

Figure 3: Efavirenz C_{max} versus Categories of Efavirenz Adverse Events (AEs)



EFV C_{max} = Efavirenz maximum concentration and AE: Adverse Events

The results suggested that there was no clear correlation between systemic exposure to EFV (C_{max}) achieved with the doses administered and the incidence of adverse events associated with the use of EFV in paediatric subjects in spite of the formulations and switch from solution to capsule formulations leading to higher EFV systemic exposures. Figure 7 includes subjects ≥ 3 years of age as well as subjects < 3 years of age. It is noted that certain adverse events, particularly psychiatric symptoms and Central Nervous System (CNS) symptoms, may be difficult to identify in infants and young children. Nonetheless, these observations were consistent with those previously reported in adults treated with EFV 600 mg. Historical data suggest that no correlation is seen between exposure and CNS side effects, and PK variability is decreased with use of the capsule. No additional precautions are warranted, other than what would be expected as normal standard of care precautions that should be taken when switching or starting any medication.

The CHMP considered that the specific safety profile of the sprinkled capsule method in children aged 3 months to 3 years is scarce. Therefore the CHMP considered necessary to provide a Direct Healthcare Professional Communication to include information and guidance for the switch of patients currently treated with Sustiva oral solution to the capsule sprinkle dosing method would solve the potential safety issue. Further detail on this can be found in section 2.5.4.

2.3.2.2. Supportive study

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"

Objective:

The primary objective of this study was to assess the bioavailability of EFV capsule contents (capsule sprinkle) mixed with applesauce, grape jelly, yogurt, or baby formula (Test treatments) relative to the intact capsule administered under fasted conditions (Reference treatment). These food vehicles were

chosen to represent a variety of typical foods given to children across a spectrum of calorie and fat content.

Study design:

Completed Phase 1 open-label, randomised, 3-period, 3-treatment crossover study balanced for residual effects in 2 treatment groups to assess the safety and bioavailability of EFV capsule contents when mixed with food vehicles or baby formula, relative to the intact capsule formulation administered under fasted conditions.

Treatment and dosing regimen:

The study included 24 subjects (healthy adult volunteers) and 21 subjects completed the study. Subjects were randomly assigned to 1 of 12 treatment sequences as follows:

Group 1 *Treatment A:* 600 mg (3 x 200 mg) EFV intact capsule (fasted)
Treatment B: 600 mg (3 x 200 mg) EFV capsule contents mixed with 2 teaspoons of applesauce.
Treatment C: 600 mg (3 x 200 mg) EFV capsule contents mixed with 2 teaspoons of Grape Jelly.

Group 2 *Treatment A:* 600 mg (3 x 200 mg) EFV intact capsule (3 x 200 mg)
Treatment D: 600 mg (3 x 200 mg) EFV capsule contents mixed with 2 teaspoons of yogurt
Treatment E: 600 mg (3 x 200 mg) EFV capsule contents mixed with 2 teaspoons baby formula.

Results and analysis:

Patient disposition

Three subjects discontinued early, 2 due to adverse events and 1 was lost to follow up.

Results

Table 9 shows the main results of the statistical analysis for the Efavirenz PK properties. EFV capsule contents mixed with all of the food vehicles assessed (applesauce, grape jelly, yogurt, and baby formula) met bioequivalence criteria for EFV $AUC_{(0-T)}$ and EFV $AUC_{(INF)}$. Bioequivalence criteria were defined as a 90% CI of the adjusted geometric mean that was completely contained within 0.80 to 1.25.

For EFV C_{max}, EFV capsule contents mixed with baby formula met bioequivalence criteria. The 90% CIs for EFV C_{max} when EFV capsule contents were mixed with applesauce and grape jelly were slightly outside the interval of 0.80 - 1.25 (the upper bound for EFV C_{max} when capsule contents were mixed with grape jelly was 1.28, while the lower bound when mixed with applesauce was 0.76); however, both CIs encompassed unity.

EFV C_{max} increased approximately 17% when EFV capsule contents were mixed with yogurt relative to the intact capsule fasted and the 90% CI was entirely above 1.

Table 9: Study AI266059 - Statistical Analysis Results for Efavirenz C_{max}, AUC_{0-T} and AUC_{inf}

PK Variable	Treatment	Adjusted Geometric Mean	Comparison	Point Estimate	90% CI
Group 1					
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
Group 2					
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

Treatments:
A = 3 x 200 mg EFV intact capsule fasted
B = 3 x 200 mg EFV capsule contents + applesauce
C = 3 x 200 mg EFV capsule contents + grape jelly
D = 3 x 200 mg EFV capsule contents + yogurt
E = 3 x 200 mg EFV capsule contents + baby formula

$AUC_{(0-T)}$ = area under the plasma concentration time curve from zero to the last quantifiable time point, AUC(INF) = area under the plasma concentration time curve from zero to infinity, CI = confidence interval, C_{max} = maximum concentration, and PK = pharmacokinetics

Conclusions from PK analysis:

The bioequivalence between the use of the capsule contents sprinkled with a variety of food vehicles and intact capsules formulation administered under fasted conditions was generally demonstrated and considered to adequately support the use of this method of administration as an alternative to the oral solution in subjects aged above 3 years of age who could not swallow the commercially available solid formulations. This was based on the rationale that PK exposure using solid formulations might be similar in adults and in children aged above 3 years. This has been recognised and accepted by the CHMP in a previous procedure (EMEA/H/C/249/II/0079).

2.3.2.3. PopPK analysis: (Study no 930057409)

Title:
"Population Pharmacokinetics Analysis of Efavirenz in Paediatric Patients".

Objectives:

- To develop a PPK model to characterise the EFV concentration-time profiles in paediatric patients infected with HIV;
- To investigate the effects of covariates on various PK parameters of EFV exposure;
- To perform an ad hoc pharmacogenomic assessment of the impact of CYP2B6 Single Nucleotide Polymorphisms (SNPs) on EFV PK;
- To conduct model-based simulations to support dose recommendations for EFV capsule sprinkles in age groups of 3 months to 18 years and EFV capsules in paediatric patients capable of swallowing capsules.

Data used

The population analysis (the PPK model) utilised PK data collected in paediatric HIV patients between 3 months and 21 years of age from the Studies PACTG 382, PACTG 1021 and AI266922 at the initiation of treatment. The data included in this PPK analysis represent all of the paediatric PK data for EFV available to the MAH up to 27 June 2011.

The Study AI266059 was also included in order to provide additional PK data. Results from this study proved bioequivalence between capsules and capsule sprinkles with regard to EFV AUC; thus, capsule and capsule sprinkles were treated as the same formulation throughout the population analysis.

After the model development was complete, the NONMEM ready PK datasets were updated. A subsequent analysis was conducted to verify the consistency between the dataset used for model development (the model development dataset) and the updated dataset. In the updated dataset, a total of 3,289 concentration records were collected from 168 paediatric patients in the PPK analysis dataset, while the Study AI266059 provided an additional 1,232 concentration records from 24 adult healthy volunteers. The paediatric trials contributed to the 88% of the subjects and 73% of the observations.

Methods

The PPK 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 software program (version VI or higher). The first-order conditional estimation method was used for estimation.

Model design and analysis

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 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.

Covariate-parameter relationships in the full-covariate model were retained in the final model provided they were statistically significant ($p < 0.001$).

A continuous covariate was considered clinically relevant if its inclusion resulted in more than a 20% change in point estimates for low (5%) and high (95%) values of the covariate and the 95% CI was outside the range of 80%-120% of the typical value of the PK parameter without this covariate (but including all other significant covariates in the model).

For a categorical covariate, the clinical relevance was defined as a 20% change in point estimates compared to the typical parameter values of the reference population and the 95% CI was outside the range of 80%-120% of the typical value without this covariate.

For both continuous and categorical covariates, covariates that resulted in a $\leq \pm$ 20% change in point estimates and a 95% CI within 20% of the reference value were determined to be not clinically important. If the point estimates of a covariate effect were within 80%-120% of the reference value, but 95% CIs exceeded the range of 80%-120%, it was concluded that there was insufficient information in the dataset.

For model evaluation, an internal posterior predictive check was performed on the final paediatric model with the model development dataset. The multivariate normal distribution was used as an approximate posterior distribution to generate 1,000 sets of population parameter values. Each set of these population parameter values was then used to simulate 1,000 datasets replicating the design, dose regimen, and covariates of the final paediatric model. Relevant summary measures (e.g., mean concentrations) were generated for both the observed and simulated data. The observed summary measure was compared to selected percentiles (5^{th}, 50^{th}, and 95^{th}) of the 1,000 simulated summary measures.

Consistency of the model development dataset and the updated dataset was confirmed by overlaying the 2 datasets with the prediction interval of the simulations. The updated dataset was used to re-run the final model to estimate parameters, find recommended doses by simulation, and evaluate pharmacogenomics information.

The final PPK model with the updated dataset was used to simulate steady-state EFV concentration-time curves at various dose regimens for the capsule sprinkle or capsule formulation in paediatric patients. This was to find dose regimens that produced comparable exposure between the paediatric patients with weight <10 kg and those with at least 10 kg with the currently approved regimen. The exposure measures used included area under the concentration-time curve in 24 hours at steady state ($AUC_{ss(0-24)}$), C_{max}, C_0 and C_{min}. The MAH proposed paediatric dosing recommendations that 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 the 10-15 kg children served as the references for C_{max} and C_0. C_{max} and C_0 were deemed comparable when the simulated values for C_{max} and C_0 for the patients with weight <10 kg were within the 80%-125% range of reference values.

Following completion of the final paediatric 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 the Study AI266922 only.

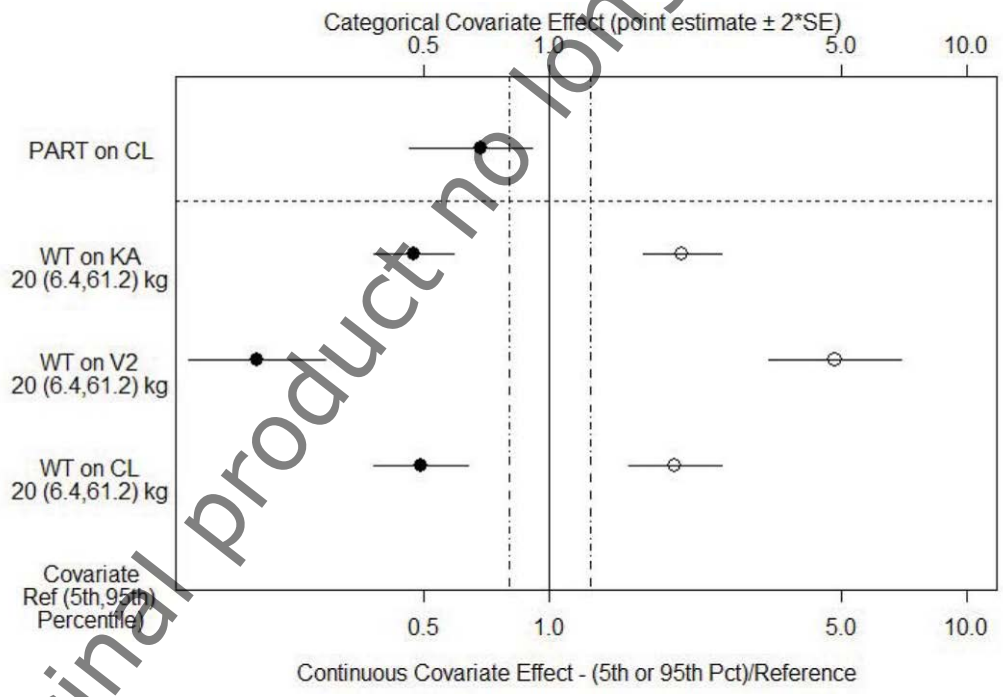
Results

The PPK of EFV in the paediatric population was well described by a first-order absorption and 2-compartment disposition model. 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 the formulation was included as part of the base structural model. Also, the oral solution formulation showed higher residual variability relative to the capsule sprinkle formulation.

The full covariate model was successfully developed, including age, weight, gender, race, previous antiviral therapy and co-medication of protease inhibitor. Both the WAM and the backward elimination methods were in agreement, and selected the covariates: weight on clearance, weight on central volume, weight on rate of absorption, and previous antiviral therapy on clearance.

The graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters are presented in Figure 4.

Figure 4: Effect of Continuous/Categorical Covariates on Efavirenz Pharmacokinetic Parameters



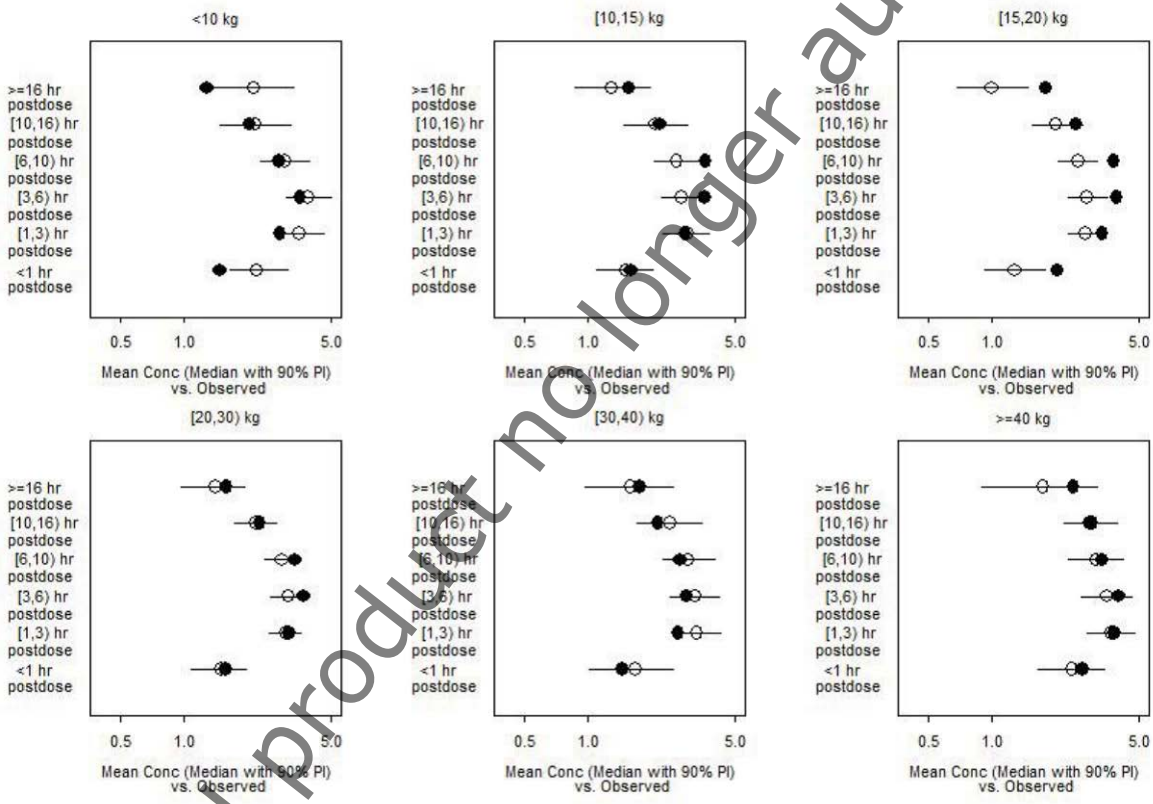
Open circles: Estimated covariate effects at the 5th percentile; closed circles: estimated covariate effects at the 95th percentile. SE = standard error; PART = previous antiretroviral therapy; CL = apparent oral clearance, KA = absorption rate constant, V2 = apparent volume of distribution in the central compartment, and WT = body weight

The estimated covariate effects were represented as the ratio of typical parameters at reference values of the covariates. The 95% CIs of these estimated effects were represented by the error bars. All of the weight covariate effects have the effect magnitude falling outside ± 20% reference value, suggesting weight may be clinically relevant. The status of previous ARV therapy (Study PACTG 1021 by design) showed a statistically significant effect; however, the upper confidence level of the magnitude was greater than (-0.2), which was inconclusive regarding clinical relevance.

Final model evaluation and predictive performance

For model evaluation, the final model predictive distributions of the geometric mean for concentrations within various time intervals were compared with the observed geometric means for the observed paediatric data. The observed geometric means for concentrations generally fell within the 5th and 95th percentiles of the predictive distribution for the final model across time intervals, and that was the case when the same comparisons were made for different weight groups (Figure 5). Based on that, it was concluded that the final model provided adequate predictive performance of the central tendency of the mean concentrations.

Figure 5: Posterior predictive check results- Observed Efavirenz plasma concentrations and 90% prediction intervals of simulated data for EFV by weight category.



Updated model

After model development was completed, additional data from Studies PACTG 1021 and AI266922 were made available. The model development dataset was subsequently updated to include the newly available data. The final model was used to simulate for the observed study designs of the updated dataset. Then, the simulated data was overlaid with the observed updated dataset. 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.

Given the consistency of the newly added data to the final model previously developed, no new model development was performed using the updated dataset. Only the base and final model were re-run using the updated data to update parameter estimates. Parameters estimates of final models with the model development dataset and the updated dataset are shown in table 10.

Table 10: 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] –	θ_8	186±15.1	188±14.9

Table 10 Parameter estimates of final models with the model development dataset and the updated dataset (cont)

Parameter [Units]		Estimate ± SE	
		Model Development Dataset	Updated Dataset
adult			
Tlag [h] - adult	θ_{14}	0.619±0.0378	0.633±0.0357
Interindividual (IIV) Random Effects			
IIV_CL	$\omega_{1,1}$	0.619	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

Simulations in order to recommend doses for children with weights <10 kg

Using the updated dataset, 100 paediatric subjects were simulated per weight category. Subject weight, which was the only covariate of subject demographics included in the final model, was sampled with replacement from the observed dataset for simulation. For each simulated subject, sampling times of 0, 1, 2, 4, 6, 8, 12, and 24 hours after a steady-state dose were created. Parametric bootstrapping was then applied using the final PK model for an internal posterior predictive check. For each simulated dataset, mean individual AUC per 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 suggested 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 [2.5 to 5 kg], respectively, appeared to produce comparable exposure to that of children weighing at least 10 kg and receiving the current authorised dosing regimens. These doses produced median AUC in the target range of 190 to 380 µM•h defined by the MAH and comparable levels to the weight groups of at least 10 kg (Table 11).

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 2.5 to 5 kg, 150 mg for 5 to 7.5 kg, and 200 mg for 7.5 to 10 kg. Table 12 and 13 show the results for simulation results of C_{max} and C_0 respectively.

Table 11: Simulation results of efavirenz mean AUC_{ss}(0-24)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
≥ 2.5 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

Table 12: Simulation results of efavirenz mean $C_{max,ss}$ 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
≥ 2.5 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

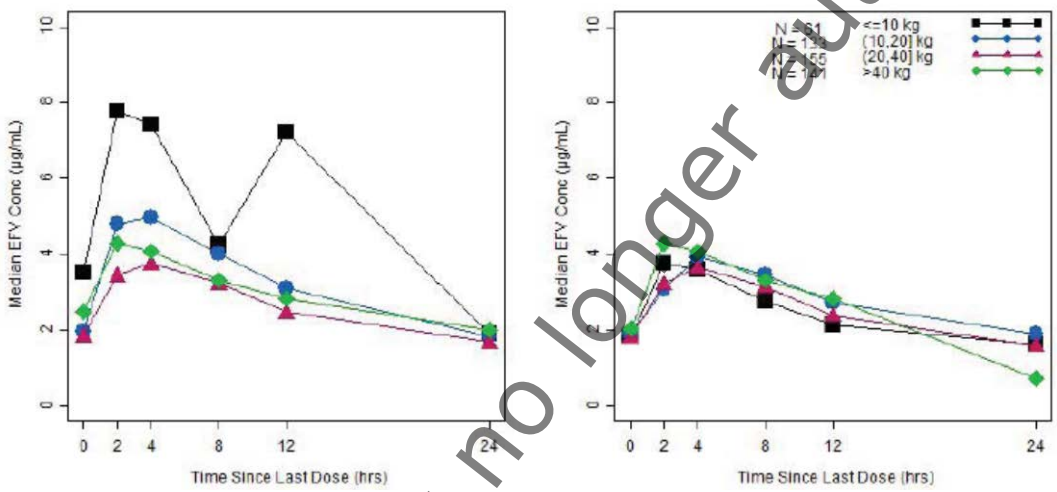
Table 13 Simulation results of efavirenz mean C_{0ss} µg/ml, 100 subjects per weight group for capsules/capsule sprinkles, 1000 simulated trials – using proposed dose regimens

Weight (kg)	Dose	10th	25th	50th	75th	90th
≥ 2.5 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

As mentioned earlier in the PPK analysis, weight was found to be a clinically important covariate on EFV exposure; age was not significant in the presence of weight.

Figure 6 visualises the effect of weight on EFV exposure using the observed concentration versus time (left panel) and the concentrations normalised to the proposed doses (right panel) for the 4 weight categories (< 10 kg, ≥ 10 to < 20 kg, ≥ 20 to < 40 kg, and ≥ 40 kg). The observed data suggested that the actual doses in the paediatric 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. With the proposed EFV doses, EFV concentration profiles appeared to be more consistent across the 4 weight groups.

Figure 6: Weight effect on median EFV concentration vs. time actual dose (left) and proposed dose (right)



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 Study AI266922 only), this evaluation was performed in an ad-hoc fashion, and one SNP at a time was tested. In this analysis, CYP2B6*6,15631GT ($p < 0.005$), CYP2B6*9,21563CT ($p < 0.005$), and CYP2B6*9,1456TC ($p < 0.05$) showed a significant improvement in the model fit.

Conclusions on the PPK model

The MAH concluded that the time course of EFV PK for the paediatric population was adequately described by a 2-compartment model with first-order absorption. It also concluded that weight was a clinically relevant covariate on EFV exposure and age was not significant in the presence of weight.

EFV exposure was associated with CYP2B6 SNPs; however, data availability was limited.

Since weight was found to be a clinically more important covariate on EFV exposure than age (age was not significant in the presence of weight), the CHMP agreed with the MAH to base the final dose recommendations for children on weight rather than age.

The simulation results supported a once daily dosing recommendation proposal for intact EFV capsules or capsule sprinkles of 100 mg for paediatric patients weighing 2.5 to 5 kg, 150 mg for 5 to 7.5 kg, and 200 mg for 7.5 to 10 kg, as comparable EFV exposure could be achieved to that with weight >10 kg, based on AUC, C_{max}, and C_0. In addition, the simulation results confirmed the current dosing recommendations for subjects weighing ≥10 kg.

Additional data provided during the assessment

During the evaluation the MAH provided upon request from CHMP the following:

- A prediction Corrected Visual Predictive Check (pcVPC) as the predictive performance regarding variability in the data was not considered sufficiently.
- The plots by different age groups and weight bands and separately for the capsule and oral solution.
- To demonstrate the model´s ability to correctly describe the central tendency and variability of PK in children below 3 years of age that received the sprinkled capsule formulation.
- Clarification on the final PPK model's ability to predict EFV PK in children less than 1 year of age as in this age range full maturation of metabolic capacity has not been reached. The use of pcVPC for this was recommended.

Consequently the MAH conducted the pcVPC to further evaluate the performance of the final PPK model (estimated with the updated data set as submitted in the original filing), with respect to age, body weight, and formulation.

The pcVPC was performed with 1,000 sets of concentration values corresponding to the observations in the PPK analysis data set that were obtained by simulation from the final PPK model. The model was evaluated by comparing the median, 5th, and 95th percentile of the observed concentration-time profile of selected sub-groups of subjects in the analysis data set, with the corresponding 90% prediction intervals obtained by simulation. The pcVPCs with respect to age, body weight, and formulation are presented in Figures 7, 8, and 9, respectively.

Figure 7: The pvVPC for efavirenz paediatric population pharmacokinetic model by age group

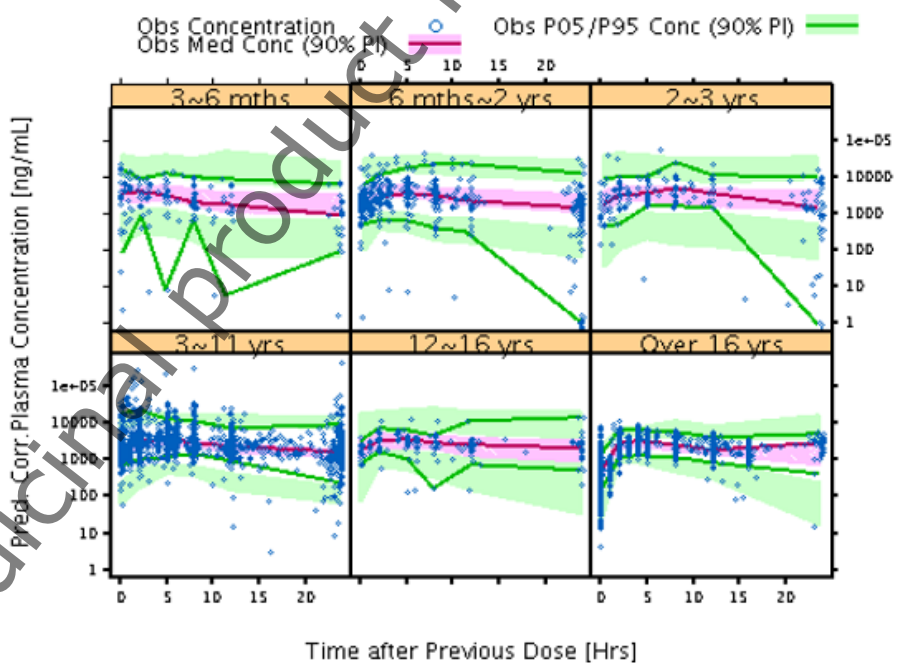


Figure 7 shows that the model adequately described the median and the 95th percentile of EFV concentration-time profile of paediatric patients in each of 6 different age groups (from 3 to ~6 months, 6 months to ~2 years, 2 to ~3 years, 3 to ~11 years, 12 to ~16 years, and > 16 years), but the 5th percentiles were less well described, especially in the 3~6 months age group. A potential reason that the observed 5% percentile was not well characterised by simulation may largely be due to the limited number of subjects (N=10) in the 3~6 months age group. The pcVPC plots for other age groups 6 months~2 years, 2~3 years, 3~11 years, 12~16 years, and > 16 years) were well characterised.

Figure 8: The pvVPC for the efavirenz paediatric population pharmacokinetic model by different weight bands

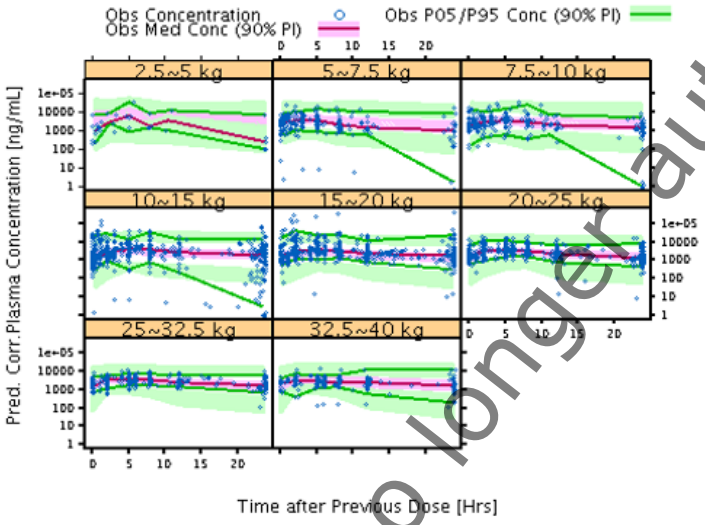


Figure 8 shows that the model provides reasonably adequate descriptions of the EFV concentration-time profile of paediatric subjects in each of different 9 weight groups (2.5 to ~5 kg, 5 to ~7.5 kg, 7.5 to ~10 kg, 10 to ~15 kg, 15 to ~20 kg, 20 to ~25 kg, 25 to ~32.5 kg, 32.5 to ~40 kg, and > 40 kg). The pcVPC plots for the lowest weight band (2.5-5kg) of paediatric subjects was not as well characterised as the rest of the weight bands, and was likely due to the low sample size (N=6) in this group.

Figure 9: The pvVPC for the efavirenz paediatric population pharmacokinetic model by capsule and oral solution

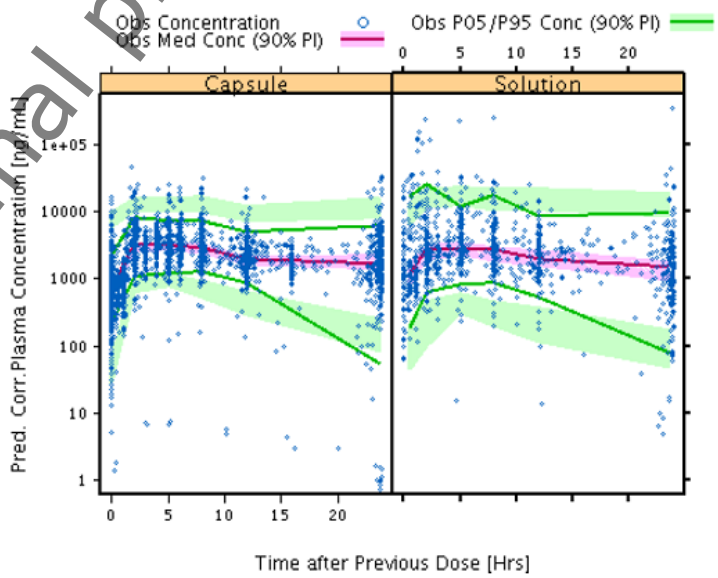
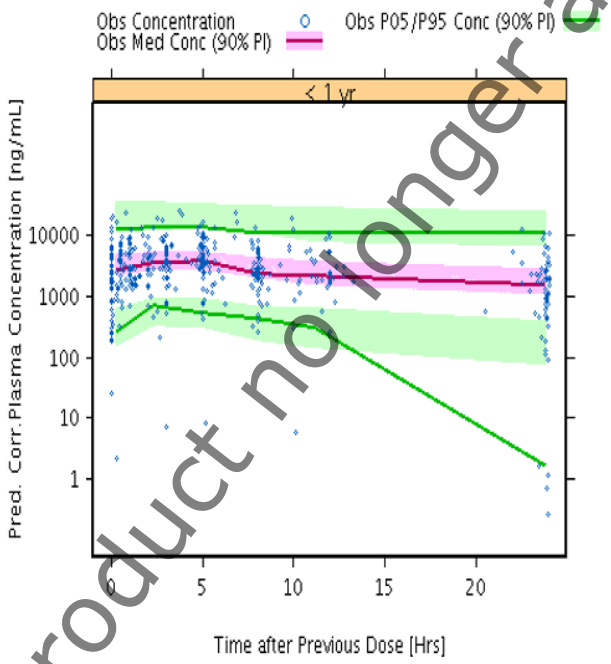


Figure 9 shows that the model adequately described the median EFV PK of paediatric subjects for different formulations (capsule or oral solution). The pcVPC plots for both formulations were well characterised, except for the median of the 95% percentile for the capsule formulation.

As requested by the CHMP, the MAH evaluated the final PPK model by using pcVPC for subjects < 1 year of age in the analysis data set. The simulation and summary of the concentration-time profiles was performed as described above and the results are presented in Figure 10.

The MAH considered that the plot shown in Figure 10 demonstrated the ability of the final PPK model to adequately describe EFV PK in children < 1 year of age for the majority of the subjects, except for the terminal phase in the 5% percentile of the observed data. This may possibly be due to sparse data collection during the terminal phase with a possible outlier.

Figure 10: Prediction – corrected VPC for updated efavirenz population pharmacokinetic model



Conclusions after provision of the additional data requested

After providing these data the CHMP agreed with the MAH that the PPK model adequately captured the EFV exposure in patients < 1 year of age and the central tendency and variability in the data, with the exception of the 5th percentile in the youngest patients which it was considered not well described. This could largely be due to the limited numbers (mn=10) in the 3~6 months age group

The CHMP considered that the model had a tendency to over predict the variability in exposure from the capsule formulation; however it was not considered as clinically relevant.

Capsule dosing recommendations:

The final PPK model was used to simulate and predict the PK parameters for efavirenz at steady state in paediatric patients (i.e. infants and children <3 years of age with body weight <10 kg). Based on this study results, the table 14 presents the recommended doses of EFV capsule (administered either as intact capsule or capsule sprinkle mixed with food) by weight ranges.

The CHMP considered acceptable the proposed capsule dosing recommendations (Table 14). These recommendations will be reflected in section 4.2 of the SmPC.

Table 14: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ µM·h	Mean C_{max} µg/mL	Mean C_{min} µg/mL
3.5-5 kg	100 mg	220.52	5.81	2.45
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

C_{max}=maximum concentration, C_{min}=minimum concentration and $AUC_{(0-24)}$= area under the plasma concentration – time curve from 0-24h

2.3.3. Pharmacodynamics

One of the aims of the Study PACTG 382 was to determine the antiviral activity of EFV in combination with nelfinavir and NRTIs. Table 15 shows the frequency distribution of subjects at week 20 with non –detectable viral loads (i.e. HIV-RNA suppression below 400 copies/mL).

The percentage of patients achieving HIV-RNA suppression below 400 copies/mL at 20 weeks of therapy in Cohort I was similar to that of Cohort II (75% vs 88%).

Table 15: Frequency Distribution of Subjects with Non-Detectable Viral Loads at Week 20 in Protocol PACTG 382

Formulation/ Cohort	Age Group ≤ 2 y	> 2 - 5 y	>5 - 12 y	>12 - 16 y	All Ages
Capsule/I	0 of 0	8 of 9 (89%)	15 of 22 (68%)	1 of 1 (100%)	24 of 32 (75%)
Solution/II	5 of 6 (83%)	6 of 7 (86%)	4 of 4 (100%)	0 of 0	15 of 17 (88%)
Either Formulation	5 of 6 (83%)	14 of 16 (88%)	19 of 26 (73%)	1 of 1 (100%)	39 of 49 (80%)

EFV doses in the protocol of the Study PACTG 382 were aimed at achieving AUCs of at least 190 µM.h, which is approximately the median AUC in adult HIV-infected subjects given a daily dose of 600 mg of the capsule formulation. The approach of targeting an AUC>190 µM.h represented a conservative strategy for EFV dosing.

Post-hoc PK- PD analysis was conducted to assess the suitability of this target range for EFV exposures. First, Week 20 EFV exposure (C_{max}, C_{min}, and $AUC_{(0-24)}$)for subjects with HIV RNA level <400 copies/mL was compared with that for subjects with HIV RNA level ≥400 copies/mL, as shown in Table 16. In both cohorts, EFV exposure for subjects with HIV RNA<400 copies/mL is higher relative to EFV exposure in subjects with HIV RNA ≥400 copies/mL.

Table 16: EFV Exposure at Week 20 for Subjects with Week 20 HIV RNA level (Last Observation carried forward [LOCF]) < 400 and ≥400 c/mL in Protocol PACTG 382

Cohort	HIV RNA level (c/mL)	Cmax (µM) GM[1] (%CV) N	Cmin (µM) GM[1] (%CV) N	AUC(0-24) (µM.h) GM[1] (%CV) N
I	< 400	18.14 (32) 24	6.54 (48) 23	255.00 (29) 23
	≥ 400	10.87 (55) 8	4.68 (28) 8	166.96 (38) 8
II	< 400	13.39 (49) 15	5.26 (74) 15	249.19 (40) 13
	≥ 400	10.27 (42) 2	1.62 (103) 2	147.76 (21) 2

[1]GM = geometric mean

To further explore this exposure-response relationship, the correlation between log (viral load drop) vs measures of drug exposure (log[AUC], log[C_{max}], or log[C_{min}]) at Week 20 was analysed. The Pearson's correlation coefficient of log viral load drop vs log AUC at Week 20, for subjects in Cohorts I and II combined, was -0.36 (P = 0.016), suggesting the existence of a weak negative correlation between the exposure variable AUC and response whereas no correlation was observed between Week 20 log viral load drop vs. log C_{max} or log C_{min} (P ≥ 0.27).

Additionally, the percentage of subjects with viral load <400 c/mL at Week 20 for various AUC ranges encompassing the 10th to 90th percentile values for adults given EFV 600 mg of the capsule formulation QD was determined. These data (combined for the 2 cohorts) are presented in Table 17.

Table 17: Frequency of Viral Suppression at Week 20 (RNA <400 c/mL: LOCF) vs EFV AUC at Week 20 in Protocol PACTG 382

AUC Range (µM•h) Number (Percentage) of Subjects with Viral Suppression				
<110	110 - 190	190 - 380	> 380	All
0 of 1 (0%)	7 of 12 (58%)	26 of 30 (87%)	3 of 3 (100%)	36 of 46 (78%)

AUC = area under the plasma concentration-time curve

As indicated in Table 17, for steady-state AUC 110 to 380 µM•h the percentage of subjects with viral load <400 c/mL was in the range of 58% to 87%. This range is comparable to response rates (approximately 46% to 88%) reported in the literature for NRTI-experienced children given HAART. The 1 patient in the PK/PD dataset with AUC <110 µM.h did not have suppressed viral load at Week 20.

Conclusions from PD analysis

The MAH concluded that higher EFV exposure (AUC) appeared to be associated with higher virologic suppression rates and that AUC range of 110 to 380 µM.h, which is observed in HIV-infected adults treated with 600 mg/day of the capsule formulation, represented a reasonable target AUC target range in children. These conclusions were endorsed by the CHMP.

2.3.4. Discussion on clinical pharmacology

The application included data from 3 main paediatric studies (Studies PACTG 382, PACTG 102 and AI266922) providing experience with EFV across a total of 182 children between the ages of 3 months and 21 years. Of these subjects, 90 received at least 1 dose of the EFV oral solution and 130 received at least 1 dose of the EFV capsules, including 41 subjects who received both formulations.

PK data from each study, as well as modelling and simulation data, bioavailability data comparing intact capsules to capsule sprinkles were provided to support the proposed paediatric dosing strategy to expand the paediatric indication for EFV to include patients 3 months to 3 years of age weighing at least 3.5kg.

Conventional pharmacokinetic parameters and data statistical analysis were used throughout the reported studies.

It is known that in HIV-infected children, selection of a dose has been complicated by age-related variations in drug clearance and a relatively wide distribution in observed clearance rates. Lower exposures in younger children may reflect both reduced bioavailability and difficulties in administering large volumes of the oral solution. Younger children appear to have a more rapid clearance of EFV, which likely leads to suboptimal exposure and the need for dose modifications in the dose-ranging studies.

The PPK of EFV in the paediatric population was well described by a first-order absorption and 2-compartment disposition model (PPK model). Diagnostic plots with the initial base model indicated differences in EFV PK between capsule sprinkles and solution.

During the PPK analysis weight was found to be a clinically more important covariate on EFV exposure than age (which was not significant in the presence of weight), therefore weight was agreed to base the final dose recommendations for children rather than age. The PPK model was used to simulate recommended doses of EFV capsule (administered either as intact capsule or capsule sprinkle mixed with food) for children <3 years of age with body weight < 10 kg (Table 14).During the assessment the MAH provided upon request from the CHMP a pcVPC to further evaluate the performance and predictive ability of EFV PK of the final PPK model and especially in children who have not reached full maturation of metabolic capacity. The CHMP considered acceptable the data provided and considered that the PPK model adequately captured the central tendency and variability in the data with the exception of the 5th percentile in the youngest patients most likely due to the limited data in that age group.

According to the PD results of Study PACTG382 a higher EFV exposure (AUC) appeared to be associated with higher virologic suppression rates. The AUC range of 110 to 380 µM.h, which is observed in HIV-infected adults treated with 600 mg/day of the capsule formulation, represented a reasonable target AUC target range in children.

- **PK in target population – Children**

EFV oral solution

The PK of EFV administered as an oral solution to paediatric subjects were investigated in the 3 main studies (Studies PACTG 382, PACTG 1021, and AI266922) summarised in section 2.3.2.1. In general, EFV exposures were suboptimal with regard to AUC in subjects < 3 years of age when EFV was administered as an oral solution.

Of the 47 subjects < 3 years of age who initiated treatment with the oral solution in the 3 main studies, 34 (72%) had an EFVAUC <190 µM•h (median AUC in adults treated with EFV 600 mg QD). The peak-to-trough ratio in subjects < 3 years of age in the 3 studies was approximately 5, a value that is about 2-fold higher than the peak-to-trough ratio observed in adults treated with 600 mg (approximately

2.3). This higher peak-to-trough ratio is indicative of the relatively higher EFV CL/F observed in younger paediatric subjects treated with the oral solution.

Greater clearance in younger children necessitated the use of higher doses to attain AUC within the target range (110 to 380 µM.h). The volumes of oral solution required to achieve target EFV AUC (>20 mL) were excessive for young subjects, particularly for those <3 years of age. Additionally, variability in EFV PK parameters was high with the oral solution, which made identification of an appropriate exposure-based dose in paediatric subjects challenging. Due to the suboptimal exposures to EFV achieved with the oral solution in subjects < 3 years of age, the oral solution was not recommended for use in this age group.

EFV capsule sprinkle:

The capsule sprinkle method of administration in the same age group consistently originated higher values for AUC, C_{max} and C_{min} and a lower clearance than with oral solution. This seemed to reflect differences mostly in the bioavailability of the two formulations and not age-related PK dependence since data from the same age group with different formulations were compared. The comparison of PK parameters between different age groups treated with capsule sprinkle was difficult due to limited number of subjects.

The Study AI266059 demonstrated the bioequivalence between intact capsules and capsule sprinkles dosing methods with food vehicles (applesauce, grape jelly, yogurt, and baby formula) in adults for EFV AUC (EFV $AUC_{(0-T)}$ and $AUC_{(INF)}$). For EFV C_{max}, EFV capsule contents mixed with baby formula met bioequivalence criteria as well. With respect to C_{max}, the 90% CIs for the co administration with grape jelly, applesauce, or yogurt were not entirely within the range of 0.80 to 1.25; however, these differences in C_{max} and C_{min} were not considered clinically relevant. This bioequivalence had already been recognised and accepted by the CHMP in a previous Sustiva variation (EMEA/H/C/249/II/0079).

In Study AI266922, most subjects <3 years of age either switched to the capsules sprinkle due to suboptimal EFV exposures with the oral solution or initiated the study with the capsule sprinkle. Of those subjects who initiated Study AI266922 with the EFV capsule sprinkle, none had an EFV $AUC_{(TAU)}$ below the minimum target of 110 µM•h. The peak-to-trough ratio for EFV in subjects <6 months of age was approximately 4.5. Similar to the oral solution, this was approximately 2-fold higher than that observed in adults treated with 600 mg EFV, indicative of higher clearance of EFV in younger subjects (i.e., infants) relative to adults.

Mean EFV C_{max} in these youngest subjects was 11,900 ng/mL. This value was markedly higher than that observed in adults treated with 600 mg, at approximately 4,000 ng/mL. Mean EFV C_{min} in infants initially treated with the capsule sprinkle was 3,320 ng/mL. Efavirenz capsule sprinkle generally produced C_{max} values that were higher than those observed after administration of the oral solution, particularly in subjects <3 years of age.

During the assessment the MAH was requested to provide a plot relating adverse events of interest from the main studies (CNS, psychiatric symptoms, rash, and liver toxicity) that occurred at a dose with an observed EFV C_{max} with EFV C_{max} values that were not associated with an adverse events of interest (i.e., no adverse events of interest was reported by that subject while being treated with the formulation and dose that yielded the observed EFV C_{max}). The data displayed (Figure 3) suggest there is no correlation between exposure to EFV achieved with the doses administered and the incidence of adverse events associated with the use of EFV in paediatric subjects. These observations were consistent with those previously reported in adults treated with EFV 600 mg. However, it was noted that certain adverse events, particularly psychiatric symptoms and CNS symptoms, may be difficult to identify in infants and young children.

The capsule sprinkle dosing method consistently showed less intra and inter-individual variability, along with a higher bioavailability relative to oral solution administration. This should improve the quality of the exposure predictions when the capsule is administered relative to the oral solution. This was in favour of the switching to capsule sprinkle in paediatric patients.

- **Bioavailability**

The bioavailability studies (Studies AI266922, PACTG 382, and PACTG 1021) showed that EFV oral solution was approximately 20% less bioavailable than the reference capsule formulation in adults.

EFV CL/F in younger children >3 months to ≤3 years of age treated with EFV oral solution was much greater than in older children (3 to 12 years of age and 13 to 21 years of age). Therefore, higher doses were required for younger children ≤3 years of age in order to achieve EFV exposures similar to those achieved in older children and adults. The negative correlation between CL/F and age was expected. The estimates of the relative bioavailability of the oral solution were substantially lower than the capsule sprinkles, particularly for Study AI266922. Bioavailability of the oral solution relative to capsule sprinkles was 35%, 5.1%, and 75% lower than the capsule formulation for Studies PACTG 382, PACTG 1021, and AI266922, respectively. In addition, the residual variability for the solution formulation was higher than capsule sprinkles (78% vs. 46%).

The MAH stated that the higher Cl/F/kg values obtained in younger children were not mainly attributable to a lower bioavailability of the oral solution (reported as 20% less bioavailable than capsules) but to the differences in age between different age groups. Initially, the CHMP noted that no other plausible explanations for these age–related differences in clearance were provided, however during the assessment pharmacogenomics turned out as a possible reason for the observed apparent age-related differences. This is further discussed under "*Consequences of possible genetic polymorphism".*

Along with a lower bioavailability a higher PK variability was observed when EFV was administered as oral solution. This suggested that different amounts of drug were absorbed when the same dose was administered. This could be related with the poor palatability of this pharmaceutical form causing regurgitation when the dose was administered. However, no significant regurgitation was reported by caregivers throughout the different the paediatric studies. A different pattern of EFV stability in the gastrointestinal tract could also be hypothesised.

Furthermore, the PopPk analysis showed not only that oral solution had lower bioavailability relative to capsule sprinkles, but the degree of lowered bioavailability with oral solution was different from study to study. The CHMP did not consider this a concern as the MAH intended to remove the oral solution from the market.

However, given the unexpected much lower bioavailability of the oral solution (specially 76% lower in Study AI266922, according to PPK analysis) and since the MAH intended to remove the oral solution from the market and thus all children will be only treated with the capsule sprinkle dosing method.

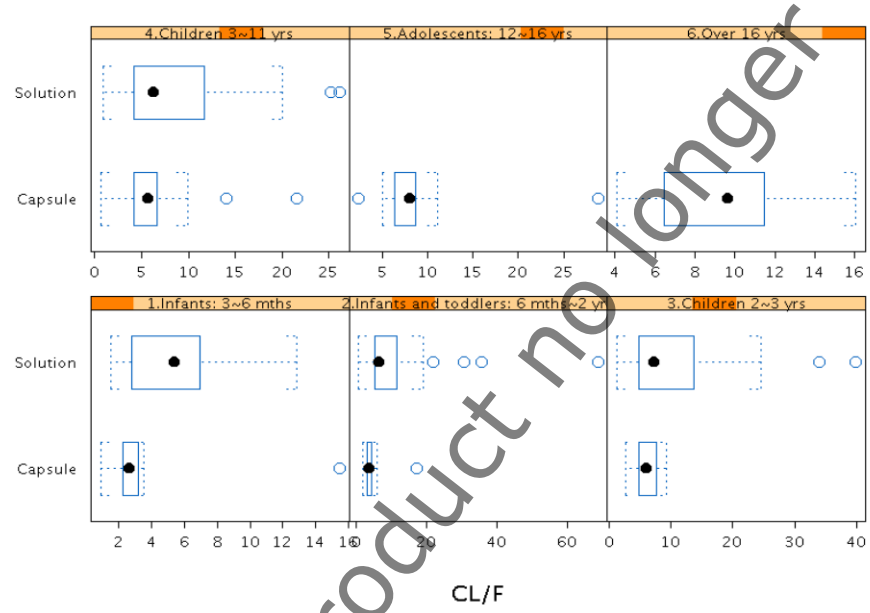
The CHMP highlighted that caution should be taken when switching from oral solution to capsules sprinkles or when comparing PK data obtained after oral solution or capsule sprinkle administration to young children as it could result in unexpected high exposure to EFV even correcting the dose to 20% less, the assumed difference in bioavailability between formulations.

The MAH was requested to propose and describe caution measures to avoid unpredictable EFV exposures when switching young children patients from oral solution to capsule sprinkle dosing method. It was agreed by both the MAH and the CHMP that a DHPC will solve this potential safety concern. This is further discussed in the corresponding section 2.5.4.

Furthermore, during the assessment the CHMP requested the MAH to estimate how much the clearance value will be influenced by that higher oral bioavailability in the reference capsule formulation sprinkled/in adults.

The MAH provided additional plots with post-hoc estimates from the EFV PPK model to show EFV CL/F for different age groups (3 months - 16 years, subdivided into smaller age ranges) following EFV oral capsule or EFV solution administration (Figure 11). The variability following solution administration was very high relative to capsule, making it difficult to speculate on trends with age for this formulation. However, the higher median EFV CL/F for solution versus capsule formulations was likely due to a lower and more variable extent of EFV absorption from the solution formulation in all of the age ranges studied. In general, subjects < 3 years of age had lower EFV CL/F following capsule administration than older age ranges.

Figure 11: Efavirenz Clearance (CL/F) by Formulation in Different Paediatric Age Ranges



After the assessment of this further data provided by the MAH, the CHMP considered that the less variable bioavailability of capsules sprinkle may contribute to the lower variability of CL/F when compared with the oral solution. Post hoc estimated from the PPK model, showed that CL/F for capsule sprinkle in children < 3 years of age was lower and less variable than in older age ranges treated with the same formulation and dosing method.

Both the MAH and CHMP agreed that the differences in the EFV systemic exposures between the formulations were most likely due to differences in their absolute oral bioavailability of EFV since EFV systemic clearance was likely not dependent on the type of formulation used to administer EFV. This was also confirmed by the post- hoc PPK analysis estimates.

- **Influence of food**

The bioavailability of a single 600 mg dose of EFV hard capsules in healthy adults volunteers was increased by 22% and 17%, respectively, when given with a meal of high fat or normal composition, relative to the bioavailability of a 600 mg dose given under fasted conditions.

According to the Study AI2666059 results, in healthy adult subjects, the efavirenz AUC when administered as the contents of three 200 mg hard capsules mixed with 2 teaspoons of certain food vehicles (applesauce, grape jelly, yogurt or infant formula) met bioequivalence criteria for the AUC of the intact capsule formulation administered under fasted conditions.

The food vehicles investigated had substantially smaller caloric contents compared to either a light meal or a high fat meal. The low caloric content of the food vehicles or baby formula is more or less analogous to fasted conditions; therefore, the minimal effects of these food vehicles on EFV exposures observed were not unexpected.

- **Consequences of possible genetic polymorphism**

Efavirenz is metabolised primarily by CYP2B6, and to a lesser extent, by CYP3A4. CYP2B6 is genetically polymorphic, with certain mutations - notably the 516 G>T substitution – reducing the enzymatic activity of CYP2B6, which may result in reduced clearance and increased plasma levels of EFV.

In paediatrics subjects from Study AI266922, the CYP2B6 516G>T mutation, among other SNPs, had a significant impact on EFV exposure. However, the higher exposures to EFV reported in subjects with the CYP2B6 516G>T mutation, could theoretically lead to concern for an increased incidence of adverse events, particularly CNS and psychiatric symptoms, rash, and liver toxicity did not appear to be associated with an increase in incidence or severity of EFV-associated adverse events.

Although individual pharmacogenetic data were only available for Study AI266922 and the sample size was small, the published literature describing the relevant pharmacogenetics in the intended population is extensive. Based on the literature describing the pharmacogenetics of the paediatric population in Study PACTG 382,and the likelihood that the demographics in Study PACTG 1021 were similar, it is likely that subjects that carried the CYP2B6 516G>T mutation were well represented in the paediatric studies as well as the paediatric PPK model and dosing simulations.

The paediatric studies and paediatric PPK model included a broad range of EFV exposures in subjects ≥3 months of age. EFV C_{max} associated with an adverse event of interest was within the range of EFV C_{max} values that were not associated with adverse events of interest, demonstrating that the higher exposures of EFV reported in subjects with the CYP2B6 516 G>T substitution did not appear to be associated with an increase in incidence or severity of EFV-associated adverse events.

Moreover based on the literature, the median $AUC_{(TAU)}$ of EFV is approximately 3-fold higher in CYP2B6 516T/T homozygotes as compared to G/G homozygotes, and is intermediate in G/T heterozygous individuals. This was part of the explanation given by the MAH to the CHMP request to clarify the apparent aberrant PK parameters results in Study PACTG382 in the age group (≥ 3 months to < 2 years) between the initial oral solution doses when calculated using the 2 algorithms. In this case, the outlier causing the different results was a subject with CYP2B6-516T/T. For further details please refer to the correspondent subsection (*Additional data provided during the assessment)* under Study PACTG382 in section 2.3.2.1.

- **Time dependencies**

Regarding PK time dependencies analysis in study PACTG 382, when comparing PK parameters from Week 2 and Week 20 PK assessment, C_{max}, C_{min}, and AUC at Week 20 appeared to be higher than the corresponding values at Week 2 but in many children a dose increase was needed in order to reach target EFV exposures and many were switched to other formulation. These changes make the comparison difficult. The relationship between Week 20 CL/F and age (r^2 = 0.20, P = 0.0008) was similar to what was observed at Week 2.

2.3.5. Conclusions on clinical pharmacology

The modelling and simulation results of the PPK analysis have demonstrated that weight-based EFV capsule/capsule sprinkle doses in paediatric subjects can provide mean EFV AUC similar to that observed in adults treated with the recommended 600 mg QD dose that has demonstrated sustained HIV suppression.

Overall, the modelling and simulation analysis, as well as observed data from paediatric Studies PACTG 382, PACTG 1021, and AI266922, supported the proposed capsule dosing recommendations (as a capsule sprinkle or intact capsule). These doses are expected to achieve AUCs within the target range demonstrated to be effective in adults.

The capsule sprinkle dosing method consistently showed less intra and inter-individual variability, along with a higher bioavailability relative to oral solution administration. This should improve the quality of the exposure predictions when the capsule is administered relative to the oral solution.

The CHMP considered that the specific safety profile of the sprinkled capsule method has not been fully evaluated in children aged 3 months to 3 years, the target population for this extension due to the limited data available on the target age group treated with capsules sprinkled.

Therefore the CHMP requested the MAH to provide a communication plan to health care professionals/prescribers upon approval of this variation to provide “information and guidance for the switch of patients currently treated with Sustiva oral solution to the capsule sprinkle dosing method would solve the safety issue.

2.4. Clinical efficacy

The efficacy of Sustiva has already been proved in the initial application and throughout is post-marketing experience (over 10 years). Therefore the data generated in this application was to produce PK data from the key studies in order to create a PPK model to construct a dosing table across all age/weight groups.

As described in section 2.3.1, 3 main paediatric studies were submitted in support of this application (Studies PACTG 382, PACTG 1021 and AI266922). These studies had already been assessed by the CHMP as part of the assessment of post-authorisation measures of Sustiva. Therefore, none of the considered main studies were originally designed to assess the efficacy of EFV administered as the sprinkled capsule contents in the target population.

The core efficacy of this application comes from the Study AI266922 since it is the only available efficacy data that has been generated in the target population using the sprinkled capsule contents as the method of administration. In addition results from a bioequivalence study (Study AI266059) was also included as a supportive study.

The relevance of these results for the assessment of efficacy of the sprinkled capsule contents method of administration in the target paediatric population must be recognised, considering the very small amount of efficacy generated in HIV infected younger children.

2.4.1. Main studies

Summary of main studies

The tables 18, 19 and 21 summarise the study design, population, therapy and efficacy results from the main studies supporting the present application for the Studies PACTG, PACTG 1021 and AI266922

respectively).

Extended detail on the objectives, treatment, dosing regimen results and analysis of these studies are detailed in section 2.3.2.1.

Study PACTG 382

None of the subjects included in the Study PACTG382 was dosed using the sprinkle capsule contents. No relevant information regarding the use of the sprinkled capsule contents could be derived from this study in the target age range.

Of note, this study was not primarily designed for efficacy evaluation.

Table 18: Summary of Study PACTG 382

Study Ref.	PACTG 382
Study Design	Phase 1/2 open-label 48-week dose-finding study that was extended to 208 weeks to assess the PK, safety, tolerability, and efficacy of EFV in combination with NFV and 1 NRTI
Study Population	ARV-naive or –experienced HIV-infected children 3 months to 16 years Total treated subjects: 102 - Cohort I: 57 subjects (3 – 16 years) - Cohort II-Strata 1: 26 subjects (≥3 months - 2 years) - Cohort II-Strata 2: 19 subjects (≥ 2 - ≤8 years)
Study Therapy	- Cohort I: EFV capsules 600 mg adjusted for body size QD - Cohort II-Stratum 1: EFV oral solution 1,200 mg adjusted for body size QD - Cohort II-Stratum 2: EFV oral solution 720 mg adjusted for body size QD
Efficacy results in overall treated Subjects (at Week 48)	- *HIV RNA < 400 c/mL* - VR-OC = 57.77 (74%) - CVR = 60/102 (59%) - Snapshot = 58/102 (57%) - *HIV RNA < 50 c/mL* - VR-OC = 44/77 (57%) - CVR = 44/102 (43%) - Snapshot = 44/102 (43%) - HIV RNA median change from baseline: -2.15 log10 c/mL - CD4 count median change from baseline: 128 cells/mm3 - CD4 percent median change from baseline: 5%

CVR: confirmed Virologic Response; VR-OC: Virologic Response-Observed Cases; NFV: nelfinavir, PK: Pharmacokinetics NRTI: Nucleoside Reverse Transcriptase Inhibitor;; EFV: Efavirenz, QD: once daily

Study PACTG 1021

The efficacy results for study PACTG1021, despite the small numbers of subjects included in each age group, are relatively more reassuring. Of note the efficacy evaluation was one of the primary objectives for this study. Efficacy results were 76.7% the overall Confirmed Virologic Response (CVR) at HIV RNA < 50 copies/ml at 48 weeks and 69.8% for snapshot. This may be considered reassuring for the treatment combination (EFV+ddI+FTC), which already had been demonstrated to have acceptable virologic efficacy in adults. Of particular note is the fact that the worst results of 50% (both for CVR and snapshot analyses) were observed for the target age Group 1 (3 months to 3 years), while there were only 6 subjects enrolled, so that the comparative efficacy rates with older age groups was not possible.

Table 19: Summary of Study PACTG 1021

Study Ref.	PACTG 1021
Study Design	Phase 1/2 open label 192-week dose finding study to assess the safety, tolerance, antiviral activity and PK of EFV in combination with FTC and ddI
Study Population	ARV-naive (or very limited ARV-exposed[1]) HIV-infected children 90 days to 21 years Total treated subjects: 43 - Group 1: 6 subjects (90 days - < 3 years) were treated for 96 weeks. - Group 2: 21 subjects (3 to < 13 years) were treated for 192 weeks. - Group 3: 16 subjects (13 - < 22 years) were treated for 192 weeks.
Study Therapy	- Group 1: initial doses of EFV oral solution for subjects < 10 kg were 390 mg QD, and subjects 10 - 32.5 kg were 600 mg QD. For subjects with AUC < threshold value, EFV capsule sprinkles were given (390 mg dose: 2 200-mg capsules; 600-mg dose: 3200-mg capsules) - Groups 2 and 3: EFV up to a maximum of 600 mg capsule or 720 mg oral solution QD
Efficacy results in overall treated subjects (at Week 48)	- *HIV RNA < 400 c/mL* • VR-OC = 34/36 (94%) • CVR = 34/43 (79%) • Snapshot = 33/43 (77%) - *HIV RNA < 50 c/mL* • VR-OC = 30/36 (83%) • CVR = 33/43 (77%) • Snapshot = 30/43 (70%) - HIV RNA median change from baseline: -2.97 log10 c/mL - CD4 count median change from baseline: 238 cells/mm3 - CD4 percent median change from baseline: 13%

[1] "very limited ARV-exposed": (i.e.received ≤ 56 days perinatal prophylaxis, or had received < 7 days cumulative ARV therapy prior to study entry
CVR: confirmed Virologic Response; VR-OC: Virologic Response-Observed Cases; ddi: didanosine , FTC: emtricitabine, PK: Pharmacokinetics; EFV: Efavirenz, QD: once daily

Study AI266922

Only 24 subjects in Study AI266922 were treated with the sprinkled capsule contents in study AI266922 (14, 7, and 3 in Groups 1, 2, and 3, respectively). Of these, only 12 (11 in Group 1 and 1 in Group 3) were initially treated with the sprinkled capsule contents and 12 also received EFV oral solution (3, 7, and 2 in Groups 1, 2, and 3, respectively).

In this study, at Week 48, viral suppression was observed across all age groups, as measured by the proportion of subjects who achieved HIV RNA < 50 c/mL and < 400 c/mL (table 20). The efficacy results in subjects who received the open capsule (sprinkle) were similar to the efficacy results for the overall study population.

Table 20: Summary of efficacy results at week 48 – Treated subjects on capsule sprinkled (Study AI266922)

	Number of Subjects (%)			
	Group 1 (≥ 3 to < 6 mos) N=13	Group 2 (≥ 6 mos to < 2 yrs) N=7	Group 3 (≥ 2 to < 3 yrs) N=3	Total N=23
HIV RNA < 400 c/mL	6/13 (46.2)	5/7 (71.4)	3/3 (100.0)	14/23 (60.9)
HIV RNA < 50 c/mL	5/13 (38.5)	4/7 (57.1)	2/3 (66.7)	11/23 (47.8)

Note: Data was from the snapshot analysis. No subjects in group4 received the capsule sprinkle

Table 21: Summary of Study AI266922

Study Ref.	AI266922
Study Design	Phase 2 open-label, 48-week dose-finding study to assess the safety, efficacy, tolerability and PK of EFV in combination with ddI and FTC. Data cut-off for Week 48 analysis: 8 February 2012; data cut-off for final analysis: 4 October 2013
Study Population	ARV-naive or experienced HIV-infected children 3 months to 6 years Total treated subjects: 37 • Group 1: 15 subjects (≥ 3 - < 6 months) • Group 2: 10 subjects (≥ 6 months - < 2 years) • Group 3: 4 subjects (≥ 2 - < 3 years) • Group 4: 8 subjects (≥3 - ≤ 6 years)
Study Therapy	EFV was given in according to a weight-based dosing nomograms, and included 1 of the following preparations in a QD dose: EFV capsules (50 and 200 mg), EFV capsule contents (50 and 200 mg) mixed with formula or a small amount of food vehicle, or EFV oral solution (30 mg/mL).
Efficacy results in overall treated subjects (at Week 48)	- *HIV RNA < 400 c/mL* • VR-OC = 21/27 (78%) • CVR = 21/37 (57%) • Snapshot = 21/37 (57%) - *HIV RNA < 50 c/mL* • VR-OC = 17/27 (63%) • CVR = 18/37 (49%) • Snapshot = 17/37 (46%) - HIV RNA median change from baseline: -3.18 log10 c/mL - CD4 count median change from baseline: 196 cells/mm^3 - CD4 percent median change from baseline: 6%

CVR: confirmed Virologic Response; VR-OC: Virologic Response-Observed Cases; ddi: didanosine , FTC: emtricitabine, PK: Pharmacokinetics; EFV: Efavirenz, QD: once daily.

2.4.2. Discussion on clinical efficacy

The efficacy data submitted to support this application, the extension of the indication to children below 3 years of age, namely for children > 3 months of age, is based on the efficacy results of three studies considered as the main studies by the MAH but which was, in fact, dose-finding studies, all of which had already been assessed by the CHMP as part of post-authorisation measures.

Moreover, none of the studies considered as main studies (Studies PACTG382, PACTG1021 and AI266922) was originally designed to assess the efficacy of efavirenz administered as the sprinkled capsule contents in the target population, which is going to be the only proposed method of administration available to infants and younger children to whom the capsules cannot be administered as the oral solution is going to be withdrawn from the market as part of this procedure.

The efficacy results from PACTG1021, as those from study PACTG382, did not even directly contribute to the efficacy assessment of the virologic efficacy of the use of the sprinkled capsule contents method of administration. These two studies actually further supported the inadequacy of the oral solution at 30 mg/ml in subjects aged below 3 years and also provided a efficacy response rate background from children in older age groups which may be used as reference for the expectable response rates in younger age groups.

The only relevant efficacy data, comparison between the oral solution and the capsules sprinkle formulations, submitted in this application is from a small subset of subjects from study AI266922 (24 subjects). However, half of these subjects had been previously treated with the oral solution and subsequently switched to the sprinkled contents strategy as they failed to achieve the target AUC of above 190 µM*h. Moreover, the Study AI266922 was not initially designed to test specifically capsule sprinkled administration, it was amended to do so, and it was conducted in a considerably experienced population.

2.4.3. Conclusions on the clinical efficacy

The available paediatric PK data was generated in three studies; PACTG 382, PACTG 1021 and AI266922, performed through the period from 1997 until 2013. The total population across studies comprise a broad age range (2.4 months to 21 years of age) and weight range (3.3 kg to 117 kg). Both efavirenz oral solution as well as sprinkled and intact capsules have been administered in different dosing regimens and in combination with other ARVs (NFV, FTC, ddI). None of these regimens are considered current state of the art. Furthermore, studies that include patients with prior antiretroviral exposure would not recommend EFV and 2 NRTIs according to present guidelines.

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV (Doc ref: EMEA/CPMP/EWP/633/02, Rev 3) and based on the identification of suitable dose regimens and the expectation that PK/PD relationship are the same in children as in adults, an extrapolation of efficacy data obtained in adults to children may be accepted.

In conclusion, the efficacy of efavirenz can be extrapolated from the adult population. Similar exposure is assumed to provide similar antiviral response. The target exposure is defined as a median AUC of 190 uM*h to 380 uM*h which corresponds to the observed median and 2xmedian exposure in adult patients treated with 600 mg QD.

The CHMP considered that the PK for bridging purposes together with the evaluation of the PPK model has acceptable results regarding its predictive performance and therefore the dosing recommendations are considered acceptable.

2.5. Clinical safety

Introduction

The safety in the target population derives from three paediatric studies (PACTG 382, PACTG 1021, and AI266922). Data from these studies were provided by study, by age group (i.e., <3 years and ≥ 3 years) and by formulation. These three clinical trial datasets provide data on a total of 182 treated children aged 90 days to 21 years.

In addition, limited data from the early access program in adult and paediatric subjects (LEAP/NPP) data available as of the 8 February 2012 database lock). Studies PACTG 382 and PACTG 1021 were completed at the time of the 8 February 2012 database lock, and provide long-term safety data (208 and 192 weeks, respectively). Table 22 shows a summary of the LEAP/NPP Studies.

As Study AI266922 was still ongoing at the time of the 08-Feb-2012 database lock, a pooled analysis providing at least 48 weeks of safety data for all subjects was performed in support of this application. Safety endpoints are presented for treated subjects during the treatment period based on an integrated database of data from Studies PACTG382, PACTG 1021, and AI266922. Results were presented by study (Studies PACTG382, PACTG 1021, and AI266922) and total, or by age group (<3, ≥3 years) and total. In addition, AEs of special interest were summarised. AEs of special interest include rash, neurologic events, and liver toxicity events.

Table 22: Summary of LEAP / NPP Studies

Study Ref.	LEAP / NPP Studies
Study Design	Ongoing Phase 3b open-label, multicentre, expanded access and named patient program to provide the EFV oral solution to HIV-infected subjects as part of their ARV regimens. Safety, tolerability, and taste were assessed. Efficacy was assessed in a substudy. Data cut-off: 1 February 2012
Study Population	ARV-naive or –experienced HIV-infected subjects Total treated subjects: 161 Paediatric subjects: 129 Adult subjects: 32
Study Therapy	EFV oral solution 200 - 600 mg (weight-based) QD
Cumulative safety	- *Treated paediatric subjects* Two subjects (1%) died, 11 subjects (9%) had SAEs, 18 subjects (14%) discontinued due to AEs, and 62 subjects (48%) had AEs. - *Treated adult subjects* 6 subjects (19%) died (all considered SAEs), 1 subject (3%) discontinued due to an AE, and 7 subjects (22%) had AEs

ARV: Antiretroviral; AE: adverse event, SAE: Serious adverse event, EFV: Efavirenz and QD: Once daily.

Patient exposure

The median time on study therapy for all subjects across the 3 studies contributing to this assessment of integrated safety was 123 weeks, with the subgroup <3 years old (n=61) having a shorter median duration of 72 weeks. The major factor contributing to this difference was the substantially smaller proportion in those < 3 years old having > 96 weeks of treatment (44% versus 65% for those ≥ 3 years).

Overall time on study therapy for the 3 paediatric studies is summarised in Table 23.

Table 23: Overall Time on Study Therapy in the Paediatric Studies (Treated Subjects)

Study therapy (weeks)	PACTG 382 (N=102)	PACTG 1021 (N=43)	AI266922 (N=37)
Mean (SE)	120.6 (8.18)	146.3 (11.92)	94.6 (12.34)
SD	82.63	78.14	75.05
Median	118.0	181.0	60.1
Min-Max	0.1-225.6	0.3-234.1	0.1-225.1

SE = Standard Error and SD = Standard Deviation

Adverse events

Adverse event by age

The overall incidence of adverse events was similar in subjects <3 years and ≥3 years (95% and 98%, respectively). In subjects < 3 years of age, the most common adverse event was diarrhoea.

The most common AEs (in ≥10% in any group) by age are summarised in Table 24.

Table 24: Most Common Adverse Events (All Grades, at Least 10% in Any Group) by Age - Treated Subjects (Studies PACTG 382, PACTG 1021, and AI266922)

System Organ Class Preferred term	Number of subjects (%) Age group		
	Age < 3 years N= 61	Age ≥ 3 years N=121	Total N=182
Any adverse event	58 (95.1)	119 (98.3)	177 (97.3)
Investigations	40 (65.6)	112 (92.6)	152 (83.5)
Infections and infestations	52 (85.2)	98 (81.0)	150 (82.4)
Otitis media	17 (27.9)	28 (23.1)	45 (24.7)
Upper Respiratory tract infection	15 (24.6)	28 (23.1)	43 (23.6)
Pneumonia	12 (19.7)	12 (9.9)	24 (13.2)
Gastroenteritis	13 (21.3)	10 (8.3)	23 (12.6)
Sinusitis	1 (1.6)	21 (17.4)	22 (12.1)
Pharyngitis	11 (18.0)	10 (8.3)	21 (11.5)
Nasopharyngitis	9 (14.8)	8 (6.6)	17 (9.3)
Body tinea	2 (14.8)	14 (11.6)	16 (8.8)
Oral candidiasis	10 (16.4)	6 (5.0)	16 (8.8)
Candida nappy rash	8 (13.1)	0	8 (4.4)
Gastrointestinal disorders	36 (59)	69 (57.0)	105 (57.7)
Diarrhoea	29 (47.5)	45 (37.2)	74 (40.7)
Vomiting	15 (24.6	23 (19.0)	38 (20.9)
Respiratory, Thoracic and mediastinal Disorders	22 (36.1)	51 (42.1)	73 (40.1)
Cough	9 (14.8)	33 (27.3)	42 (23.1)
Rhinorrhoea	4 (6.6)	13 (10.7)	17 (93.)
General disorders and administration site conditions	15 (24.6)	45 (37.2)	60 (33.0)
Pyrexia	13 (21.3)	34 (28.1)	47 (25.8)
Nervous system disorders	9 (14.8)	35 (28.9)	44 (24.2)
Headache	1 (1.6)	17 (14.0)	18 (9.9)
Eye disorders	10 (16.4)	22 (18.2)	32 (17.6)
Conjunctivitis	9 (14.8)	13 (10.7)	22 (12.1)
Skin and subcutaneous disorders	29 (47.5)	61 (50.4)	90 (49.5)
Rash	10 (16.4)	20 (16.5)	30 (16.5)
Dermatitis diapper	13 (21.3)	1 (0.8)	14 (7.7)

Adverse event by EFV formulation

Overall rates of adverse events were similar for subjects who received the EFV capsule sprinkle and oral solution (96% each). Among subjects who received the oral solution, the most common adverse event was diarrhoea.

The adverse event category of gastrointestinal disorders was considered of most interest, as these adverse events are most likely to show an association with the formulation administered. Both the overall rates for gastrointestinal events and the rates for adverse events diarrhoea, vomiting, abdominal pain, nausea, and gastritis were generally comparable across the two formulations (oral solution versus capsules).

The most common adverse events (in ≥10% in any group) by EFV formulation are summarised in Table 25.

Table 25: Most Common Adverse Events (All Grades, at Least 10% in Any Group) by EFV Formulation – Treated Subjects (Studies PACTG 382, PACTG 1021, and AI266922)

System Organ Class Preferred term	Number of subjects (%) EFV formulation group		
	Capsules N= 132	Oral solution N=90	Total* N=182
Any adverse event	126 (95.5)	86 (95.6)	177 (97.3)
Investigations	107 (81.1)	65 (72.2)	152 (83.5)
Infections and infestations	98 (74.2)	71 (78.9)	150 (82.4)
Otitis media	24 (18.2)	24 (26.7)	45 (24.7)
Upper Respiratory tract infection	29 (22.0)	15 (16.7)	43 (23.6)
Pneumonia	12 (9.1)	12 (13.3)	24 (13.2)
Gastroenteritis	9 (6.8)	14 (15.6)	23 (12.6)
Sinusitis	19 (14.4)	3 (3.3)	22 (12.1)
Pharyngitis	13 (9.8)	8 (8.9)	21 (11.5)
Nasopharyngitis	11 (8.3)	9 (10.0)	17 (9.3)
Impetigo	8 (6.1)	9 (10.0)	17 (9.3)
Gastrointestinal disorders	65 (49.2)	49 (54.4)	105 (57.7)
Diarrhoea	42 (31.8)	36 (40.0)	74 (40.7)
Vomiting	19 (41.4)	19(21.1)	38 (20.9)
Respiratory, Thoracic and mediastinal Disorders	22 (36.1)	27 (30.0)	73 (40.1)
Cough	27 (20.5)	16 (17.8)	42 (23.1)
General disorders and administration site conditions	41 (31.1)	20 (22.2)	60 (33.0)
Pyrexia	31 (23.5)	16 (17.8)	47 (25.8)
Nervous system disorders	35 (26.5)	9 (10.0)	44 (24.2)
Headache	16 (12.1)	2 (2.2)	18 (9.9)
Eye disorders	21 (15.9)	11 (12.2)	32 (17.6)
Conjunctivitis	16 (12.1)	6 (6.7)	22 (12.1)
Skin and subcutaneous disorders	62 (47.0)	35 (38.9)	90 (49.5)
Rash	21 (15.9)	9 (10.0)	30 (16.5)
Dermatitis diapper	4 (3.0)	11 (12.2)	14 (7.7)

*Since some subjects switched formulation, the total N may be < sum of the Ns for each formulation

Additional data provided during the assessment

Upon request of the CHMP, an analysis using the combined safety data from Studies AI266922, PACTG 382, and PACTG 1021 using patient exposure years as the denominator and patients' time under each formulation (whole capsule, oral solution, and capsule-sprinkle) was performed. All adverse event reports (not just the first onset) under each formulation according to the formulation being taken at the time of onset were counted in the analysis. The overall number of subjects specifically on capsule-sprinkle in the clinical trial data set was relatively small (n=27) compared to the larger number of subjects taking whole capsules and oral solution. Due to the fact that capsule-sprinkle was introduced later in the development program, and because younger subjects in Study AI266922 were required to initiate therapy with oral solution, the patient-year exposure to capsule-sprinkle was correspondingly smaller (39.6 patient-years) to that for the other formulations.

Overall, the incidence rate/100 patient-years of adverse events were similar for subjects who received the EFV whole capsule, oral solution, and capsule-sprinkle (634.0, 720.5, and 760.1, respectively), keeping in mind that comparisons were limited due to the smaller sample size for capsule-sprinkle. Upon review across System Organ Classes (SOCs), subjects on capsule-sprinkle appeared to have a somewhat higher rate of infections, driven primarily by typical childhood infections of upper respiratory infections and sinusitis. Since the oral solution is known to be poorly palatable, attention is given to the gastrointestinal SOC that reveals a slightly higher rate of gastrointestinal events, driven primarily by slightly higher rates of vomiting among subjects on oral solution. Nervous system symptoms may be difficult to detect in younger subjects, making comparisons problematic for this category. Summary of comparative safety across EFV formulation of events coded to the different SOC expressed by incidence rate per person/years is shown in Table 26.

Serious Adverse Events (SAEs) / deaths / other significant events

The incidence of SAEs was higher in subjects <3 years (46%) than in subjects ≥3 years (26%). In subjects <3 years, the most common SAEs were pneumonia, neutropenia, and gastroenteritis. In subjects ≥3 years, the most common SAEs were maculo-papular rash, rash, and neutropenia.

One treated subject died of staphylococcal sepsis > 1 year after the last dose of study medication in Study PACTG 382. The death was not considered related to study drug by the investigator. No death were observed in Study PACTG 1021, while in Study AI266922 (Week 48 analysis cut-off 8 February 2012), two treated subjects had died. None of these deaths was considered related to the study therapy by the investigators.

There were 3 categories of adverse events of special interest analysed: neurologic events, rash, and liver toxicity. The incidence of neurologic events was lower in subjects <3 years than in subjects ≥3 years (5% vs. 22%). In subjects <3 years, all neurologic events were reported in less than 1 subject each, and none had any adverse events coded to the SOC of Psychiatric Disorders. In subjects ≥3 years, the most common neurologic events were dizziness, insomnia, and nightmare.

The overall incidence of rash was 30% in subjects <3 years and 33% in subjects ≥3 years. In subjects <3 years, the most common rash events were rash, maculo-papular rash, and skin reaction. In subjects ≥3 years, the most common rash events were rash, maculo-papular rash, and papular rash. The median time to onset of rashes that were classified as being consistent with drug-related rash (based on the Medical Dictionary of Regulatory Activities [MedDRA] preferred term coding) was 27 days. Of note, the time to rash differed across the 2 age groups, with the median time to rash being 87 days for those < 3 years and 11 days for those ≥3 years.

In all 3 studies, the most common adverse events of liver toxicity were the laboratory abnormalities Alanine Transaminase (ALT) increased and Aspartate Aminotransferase (AST) increased. The incidence of events of liver toxicity was lower in subjects <3 years (21%) than in subjects ≥3 years (42%). Across the 3 studies, no subjects met the criterion for potential Drug Induced Liver Injury (DILI).

Table 26: Comparative results for the different System Organ Class(SOC) in terms of the Incidence Rates (IR) /100 per year (p.y.):

Cases per pharmaceutical formulation	Capsules		Oral Solution		Capsule Sprinkle	
	N = 105		N = 90		N = 27	
SOC	**No Cases**	**IR/100 p.y**	**No Cases**	**IR/100 p.y**	**No Cases**	**IR/100 p.y**
Any adverse event	1483	630,4	1080	720,5	301	760,1
Investigations	533	227,9	389	259,5	20	50,5
Infections and infestations	324	138,5	283	188,8	153	386,4
Gastrointestinal disorders	147	62,8	132	88,1	26	65,7
Respiratory, Thoracic and mediastinal Disorders	107	45,7	66	44	18	45,5
Skin and subcutaneous disorders	90	38,5	68	45,4	33	83,3
General disorders and administration site conditions	51	21,8	32	21,3	11	27,8
Nervous System Disorders	46	19,7	19	12,7	8	20,2
Blood and Lymphatic System Disorders	27	11,5	23	15,3	3	7,6
Eye disorders	25	10,7	13	8,7	7	17,7
Psychiatric Disorders	21	9	10	6,7	0	0
Injury, Poisoning and Procedural Complications	13	5,6	8	5,3	7	17,7
Musculoskeletal and Connective Tissue Disorders	18	7,7	7	4,7	2	5,1
Ear and Labyrinth Disorders	9	3,8	9	6	3	7,6
Reproductive System and Breast Disorders	16	6,8	4	2,7	0	0
Renal and Urinary Disorders	16	6,8	2	1,3	0	0
Metabolism and Nutrition Disorders	6	2,6	5	3,3	4	10,1
Hepatobiliary Disorders	10	4,3	2	1,3	1	2,5
Neoplasm Benign, Malignant and Unspecified	9	3,8	1	0,7	0	0
Vascular Disorders	5	2,1	1	0,7	2	5,1
Congenital, Familial and Genetic Disorders	1	0,4	5	3,3	1	2,5
Immune System Disorders	3	1,3	0	0	2	5,1
Pregnancy, Puerperium and Perinatal Conditions	4	1,7	0	0	0	0
Cardiac Disorders	1	0,4	0	0	0	0
Endocrine Disorders	0	0	1	0,7	0	0
Surgical and Medical procedures	1	0,4	0	0	0	0

IR: Incidence Rate, p.y.: per year; N: Number of cases

Laboratory findings

Generally, Grade 3 - 4 haematology and serum chemistry abnormalities were low across the 3 paediatric studies, except for abnormal neutrophils, which were present in > 10% of subjects across all 3 studies, and were higher in Studies PACTG 382 and PACTG 1021 (33% and 30%, respectively) than in AI266922 (16%). This cross-study difference may reflect the different durations of observation across the 3 studies.

Among subjects < 3 years, Grade 3 - 4 abnormalities in ≥ 5% of subjects were neutrophils + bands (relative) (37%), total cholesterol (6%), and ALT (5%). Among subjects ≥3 years, Grade 3 - 4 abnormalities in ≥5% of subjects were neutrophils + bands (relative) (25%) and total cholesterol (8%).

The incidence of abnormalities varied across age groups within each study; however, because of the small sample sizes in each age group, no overall conclusions can be drawn from these data.

Clinical Laboratory Evaluations by Age

Haematology

Among subjects < 3 years, the only Grade 3 - 4 hematologic abnormality in ≥5% of subjects was neutrophils + bands (relative) (21 of 57 subjects [37%]); all other Grade 3 - 4 hematologic abnormalities were reported in ≤ 2 subjects each.

Among subjects ≥3 years, the only Grade 3 - 4 hematologic abnormality in ≥ 5% of subjects was also neutrophils + bands (relative) (30 of 119 subjects [25%]); all other Grade 3 - 4 hematologic abnormalities were reported in ≤ 2 subjects each.

Liver Function Tests

Among subjects < 3 years, the most common Grade 3 - 4 liver function abnormalities were ALT (3 of 58 subjects [5%]) and total cholesterol (3 of 55 subjects [6%]); all other Grade 3 - 4 liver function abnormalities were reported in ≤ 2 subjects each.

Among subjects ≥ 3 years, the most common Grade 3 - 4 liver function abnormalities were total cholesterol (9 of 119 subjects [8%]) and ALT (4 of 119 subjects [3%]); all other Grade 3 - 4 liver function abnormalities were reported in ≤2 subjects each.

Other Serum Chemistries

Among subjects < 3 years, all Grade 3 - 4 serum chemistry abnormalities were reported in ≤ 2 subjects each.

Among subjects ≥ 3 years, Grade 3 - 4 low serum glucose was reported in 4 of 117 subjects (3%); all other Grade 3 - 4 serum chemistry abnormalities were reported in ≤ 1 subject each.

Discontinuation due to adverse events

Across the 3 paediatric studies, the overall incidence of discontinuation of study therapy due to adverse events was low (8%), and was similar in subjects <3 years and ≥3 years (8% each). The most common adverse events leading to treatment discontinuation is presented in Table 27.

Table 27: Most Common Adverse Events Leading to Discontinuation of Study Therapy (at least 2 subjects in any group) by Age - Treated Subjects (Studies PACTG 382, PACTG 1021, and AI266922

System Organ Class Preferred term	Number of subjects (%) Age group		
	Age < 3 years N= 61	Age ≥ 3 years N=121	Total N=182
Any adverse event	5 (8.5)	10 (8.3)	15 (8.2)
Gastrointestinal disorders	3 (4.9)	2 (1.7)	5 (2.7)
Diarrhoea	3 (4.9)	1 (0.8)	4 (2.2)
General disorders and administration site conditions	1 (1.6)	2 (1.7)	3 (1.6)
Pyrexia	0	2 (1.7)	2 (1.1)
Skin and subcutaneous disorders	0	6 (5.0)	6 (3.3)
Rash	0	3 (2.5)	3 (1.6)
Rash maculo-papular	0	3 (2.5)	3 (1.6)

Post marketing experience

CARES Database - MAH CARES Search 1 (cumulative through 2 May 2012)

To supplement the clinical trial safety data, a search of the MAH Corporate Adverse Event Reporting System (CARES) database was conducted to ensure the inclusion of all available safety data for children in the 3 month to 3 year age range, in support of this application. The cumulative search covered all EFV reports received through 2 May 2012. In order to avoid duplication of data, this search excluded cases reported from Studies PACTG 382, PACTG 1021, and AI266922. Otherwise, the search included all reports from studies other than these 3 paediatric studies, as well as all spontaneous reports, and all literature-derived reports.

Results identified 13 unique cases, including 3 cases of events of special interest for EFV (1 each of rash, insomnia, and increased transaminases). The remaining 10 cases included a majority of infection-related events (n=6; 5 from South Africa and 1 from Thailand), consisting of 2 lower respiratory tract infections, 1 pneumonia, 1 pulmonary tuberculosis (TB) , 1 fatal sepsis in association with diarrhoea, and 1 case of herpes zoster pneumonia that resolved with acyclovir treatment. The remaining 4 reports included 1 each of urticaria and bronchospasm, both of which resolved apparently without sequelae, 1 accidental exposure (without sequelae), and 1 case of Guillain-Barre Syndrome (GBS) that had complete resolution after 4 weeks. In 3 of the 13 cases, immune reconstitution syndrome was invoked as a probable complicating factor (herpes zoster pneumonia, pneumonia, and GBS). Five of the 10 reports came from non-MAH studies (4 from a single study in South Africa, including the 2 lower respiratory tract infection cases, the pneumonia case, and the herpes zoster case; and the single pulmonary TB case was from another study in Africa). Two of the 13 reports derived from the literature (the fatal sepsis with diarrhoea case and the GBS case).

With respect to the 3 events of special interest, the rash was reported as being maculo-papular in character, involving the entire body and associated with “pink eyes and swollen lips” as well as pyrexia; onset was 1.5 weeks after initiation of therapy. Resolution occurred rapidly over the week following discontinuation of therapy, and involved desquamation. The case of insomnia occurred in a 2-year-old and resolved when dosing was adjusted to administer EFV in the morning instead of the evening. The transaminitis report provided very limited information, but interruption of drug was associated with resolution, and hepatitis A serology was positive, although the temporal relationship of the serology to the event was not clear.

In summary, the review of these 13 incremental reports from the CARES database indicated that all cases were consistent with the types of clinical events already documented in the 3 clinical study datasets

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

MAH CARES Search 2 (3 May 2012 till 4 October2013)

To supplement the clinical trial safety data presented in this application, including long-term data from Study AI266922, a second search of the MAH CARES database was conducted. The second search used the same criteria as the first search, and covered all EFV reports received from 03-May-2012 through 04-Oct-2013. Four additional cases were identified for which the CIOMS reports for these cases have been submitted for assessment.

Literature Review - Literature Search 1 (1998 till 31 March 2012)

A literature search was conducted in order to assess all identifiable citations referring to the use of EFV in paediatric population since the last literature search was done in 1998. The current search covers literature available online before 31 March 2012; the search was conducted for 2 time periods: initiation of EFV trials to 24 June 2009 and from 1 January 2009 to 28 March 2012.

Databases used were MedlineR, Derwent Drug Files, Excerta Medica, Biosis PreviewsR, ToxFile, SciSearchR, CA SearchR, Adis Clinical Trials Insights, Adis R&D Insight, Int.Pharm.Abs, EMBASE, and EMBASE alert. Duplicates were identified and accounted by manual review and endnote application. The results may include items that were cited in the prior search, but have references that have been updated since that search. The search was limited to the paediatric population and executed by the IKI Literature Services Department of the MAH. A comprehensive search strategy was used with the key words “Sustiva,” “efavirenz,” “BMS-561525,” “Patent 5,519,021,” and “Patent 5,663,169,” as well as truncated versions and various derivations of these terms to capture citations generated within the above-mentioned time period. Overall, 294 clinical trials/abstracts and nonclinical articles/abstracts were reviewed.

In conclusion, the literature search identified no additional information on clinical trials on safety and effectiveness, clinical trials on new uses, clinical pharmacology studies, and reports of clinical experience pertinent to safety.

Literature Search 2 (15 March 2012 till 1 November 2013)

To supplement the clinical trial safety data presented in this summary, including long-term data from Study AI266922, a second literature search was conducted. The second search used the same criteria as the first search, and covered the period of 15 March 2012 till 1 November 2013.

In conclusion, the literature search identified no additional information on clinical trials on safety and effectiveness, clinical trials on new uses, clinical pharmacology studies, and reports of clinical experience pertinent to safety.

2.5.1. Discussion on clinical safety

Safety data in the paediatric population aged 3 months to 3 years was limited to 61 subjects. Only 24 subjects in study AI266922 were treated with the sprinkled capsule contents, of which 12 also received EFV oral solution. Formal analyses and comparisons between age groups and treatment groups were limited.

The comparison provided was in relation to the overall rate of adverse events reported for subjects treated with either the oral solution or the sprinkled capsule contents, which are similar and reported at

an overall rate of 96%. Subsequent tabulations of the observed rate of reporting of adverse events of different severity only compared the oral solution with the capsules without regard to whether they were administered as a whole or with the sprinkle method.

The safety profiles of the capsules administered be either method may not differ significantly, although issues of tolerability to the taste or other organoleptic characteristics of the capsule contents could have an impact on its tolerability. From observed data, vomiting has been more frequently reported across the 3 studies for the oral solution than for the capsule (21% vs 14%), although the reported rates of nausea have been similar for both formulations (4.4% and 5.3%, respectively, for the capsules and for the oral solution). These data provided did not take into consideration any potential variation in the incidence rates with age, as the oral solution was used mostly in subjects aged 3 years or less and the capsules were used in subjects aged up to 22 years.

Most of the reported events were in the category of Investigations, as would be expected in studies including a considerable proportion of paediatric subjects with congenitally acquired HIV infection. No notable differences comparative to the safety profile of the drug in the paediatric population have been detected. Of note and of major relevance for the assessment of the current procedure, no major differences could be detected in the overall incidence of adverse events in children aged 3 months to 3 years (N=61) or in older children. Therefore, whereas the number of exposed subjects in the younger age-group is very small and most of them have been treated with oral solution formulations and only 24 with the sprinkled capsule contents, no signal indicating a different safety profile could be detected in the submitted safety data.

Additional analysis reflecting the duration of exposure, such as in patient/years was deemed necessary. This analysis requested during the assessment provided reassurance on the safety profile of efavirenz in target age group of this extension of the indication.

The overall safety profile does not differ from the one that had been previously assessed, based mostly on the same data, and which is already reflected in the SmPC. However there is still an uncertainty of the long term potential undesirable effects such as the long term neurocognitive development in children. This was included as an important and potential risk or missing information in the RMP version 6.1 subject to ongoing signal evaluation.

2.5.2. Conclusions on clinical safety

In conclusion, despite the small safety dataset did not point to any new or unexpected safety signal or characteristic in the overall population. The specific safety profile observed with the sprinkled capsule method in the target population along with data from the adult study AI266095 provided sufficient reassurance to conclude that does not differ from the one already well known for EFV.

2.5.3. PSUR cycle

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5.4. Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is considered necessary for the safe and effective use of the product and aims at warning Healthcare professionals that switching patients from oral solution to capsule sprinkle method may result in higher drug exposures; therefore, patients should be monitored closely for evidence of Sustiva toxicity during the transition period.

The DHPC is provided in Attachment 10 together with the communication plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent within 2 months after CHMP Opinion, unless agreed differently with NCAs to healthcare professionals treating paediatric HIV patients in the Member States where Sustiva Oral Solution is currently available (i.e., France, Germany, Ireland, Italy, Spain, and United Kingdom).

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is provided in attachment 9.

Summary of Safety Concerns

The PRAC rapporteur is of opinion that the safety specifications of the below table are considered acceptable. 'Long term neurocognitive development in children' has been duly added to the RMP as missing information.

Important identified risks	
Psychiatric and Nervous System Symptoms	Psychiatric adverse reactions have been reported in patients treated with EFV. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behavior.
Skin rash and severe skin reactions	Mild-to-moderate rash has been reported in clinical studies with EFV and usually resolves with continued therapy. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of adult patients treated with EFV. The incidence of Grade 4 rash (e.g., erythema multiforme, SJS) in adult patients treated with Sustiva in all studies and expanded access was 0.1%. In children, rash reported in 58 of 182 children (32%) in 3 clinical trials for a median of 123 weeks, and was severe in 6 children (3%).
High-grade hepatic enzyme elevations and severe hepatic events	Most hepatic enzyme elevations are asymptomatic. Since the clinical hallmark of hepatitis is elevated liver enzymes, elevations in the range generally associated with hepatitis must be monitored. Patients with underlying liver disease should be assessed regularly for prevention of potential liver injury. A few of the post-marketing reports of hepatic failure occurred in patients with no preexisting hepatic disease or other identifiable risk factors. Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.
Fetal neural tube abnormalities (including meningomyelocele, spina bifida, or hydrocephalus) associated with first trimester exposure to EFV	Malformations were observed in 3 of 20 fetuses/newborns from EFV-treated cynomolgus monkeys. Anencephaly and unilateral anophthalmia were observed in one fetus, micro-ophthalmia in another fetus and cleft palate in a third fetus. EFV induced fetal resorption in rats. As of 31-Jan-2011, the APR has received 18 reports of defects in 735 infants with first trimester exposure to EFV, including a single case of myelomeningocele and single case of anophthalmia with severe oblique facial clefts and amniotic banding.
Alteration in EFV blood levels and CYP2B6 genetic polymorphisms.	Clinical trials indicated EFV plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isozyme. Post-marketing reports of patients with CYP2B6 genetic polymorphisms and reduced drug clearance of EFV.

Important potential risks	
Urolithiasis / Nephrolithiasis	Serious and non-serious reports of renal lithiasis related events have been reported in patients treated with EFV; the majority reports were confounded by a prior history of urolithiasis and/or concomitant exposure to other drugs with lithogenic potential. A few literature reports identified renal stones with EFV-containing metabolites. There were no reports with a fatal outcome. Cases of nephrolithiasis have been reported during post-marketing surveillance in HIV infected patients receiving EFV therapy. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made in the post marketing reporting system.
Malignant neoplasms	The potential human risk of malignancy related to use of EFV-containing products does not appear to be measurably increased compared to other ARVs and no evidence of a signal for increased risk of malignancy in patients using these products has been established. No evidence for increased risk of malignancy in patients using these products
Exacerbation of Sustiva-related AEs when switching from oral solution to capsule sprinkle	Capsule sprinkles offer a more consistent bioavailability across all age groups, including children aged 3 months to 3 years. However, because of the increased bioavailability and intersubject variability, higher exposures may result when switching from oral solution. Therefore, patients should be monitored closely for evidence of Sustiva toxicity during the transition period from oral solution to capsule sprinkle. While no new toxicities have been identified in patients taking capsule sprinkle, the potential exists for an increased frequency of known AEs, particularly in the first few weeks of therapy. Because young children may not be able to report these toxicities, close clinical monitoring is warranted.
Missing information	
Use in pediatric populations	EFV has not been evaluated in children < 3 months of age or who weigh <3.5 kg. Therefore, EFV should not be given to children < 3 months of age.
Use in elderly populations	Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.
Patients with renal impairment	The PK of EFV have not been studied in patients with renal insufficiency; however, less than 1% of an EFV dose is excreted unchanged in the urine, so the impact of renal impairment on EFV elimination should be minimal. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.
Patients with hepatic impairment	Patients with mild liver disease may be treated with their normally recommended dose of EFV. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. EFV is not recommended for patients with moderate hepatic impairment and must not be used in patients with severe hepatic impairment (CP Class C).
Development of neurocognitive changes in HIV-infected children	Neurocognitive deficits are more common in HIV-infected patients than HIV-uninfected patients, regardless of ART status or disease state, in many, but not all, studies. HIV associated neurocognitive disorders (HAND) are primarily characterized by subcortical dysfunction, with memory and psychomotor speed impairment, depressive symptoms, and movement disorders; this is in accordance with pathology suggesting that HIV affects predominantly subcortical and deep grey matter structures. The deficits associated with HAND may wax and wane over time, unlike the progressive neurological decline seen in other neurodegenerative diseases, such as Alzheimer disease. Selection of an ART regimen for patients suspect for HAND should be optimized to the resistance profile of plasma virus and to minimize toxicity or intolerance; there may be added benefit from the selection of a treatment regimen that is optimized for CNS penetration. Little is known about the potential susceptibility of children to the symptoms of HAND that have been described only in adults. There are no adverse neurocognitive signals in children treated with EFV with regard to the increased risk for potentially irreversible CNS changes associated with HAND. EFV can be used safely in children when following the neuropsychiatric precautions in the product label. The MAH will continue to monitor neurocognitive changes in children treated with EFV.

Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

The PRAC rapporteur is of opinion that routine PV is sufficient to monitor the main issue related to the paediatric use. The below Pharmacovigilance Plan is acceptable.

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
D:A:D study is a prospective multi-cohort study of HIV-infected persons under active follow up	To understand the association between exposure to ARV drugs and the risk of CVD, CLD (liver failure, liver transplantation, or liver-related death), ESRD (need for permanent dialysis or kidney transplantation) or death caused by chronic kidney failure, and non-AIDS-related malignancies	Myocardial infarction, CVD, CLD, and ESRD	Data mergers for the collaborative epidemiologic D:A:D study happen every year, and submission of a report to the EMA follows in the second quarter of each year. The HAART-OC has agreed to continue funding the D:A:D study for a further 4 years until 2017 (17th data merger). Funding will not continue past this point. EMA questions (which the HAART OC funds the D:A:D study to answer) are endpoint driven, and in 2017, should have been answered with reasonable statistical power, and thus, regulatory closure will have been met.	As determined by HAART Oversight Committee
Antiretroviral Pregnancy Registry	To detect any major teratogenic effects involving any of the Registry drugs, including EFV, to which pregnant women are exposed.	Teratogenicity of Registry drugs, including EFV.	The APR, an observational, exposure registration and follow-up study was established in Jan-1989 to monitor major teratogenic effects of any ARV drug exposure during pregnancy.	Interim reports are issued by the APR in June and December each year and the most current data available are included in PSUR/PBRER submissions.

Summary of Risk Minimization Measures

The PRAC Rapporteur, having considered the data submitted and the MAH's responses to the RSI, is of the opinion that the risk minimisation measures of the updated RMP (including the DHPC as an additional risk minimisation measure regarding the risk of exacerbation of Sustiva-related AEs when switching from oral solution to capsule sprinkle) are sufficient to minimise the risks of the product in the new proposed indication.

Safety Concern	Risk Minimization Measures	
	Routine	Additional
1. Psychiatric and Nervous System Symptoms	Routine PhV	None
2. Skin rash and severe skin reactions	Routine PhV	None
3. High-grade hepatic enzyme elevations and severe hepatic events	Routine PhV	None
4. Fetal neural tube abnormalities (including meningomyelocele, spina bifida, or hydrocephalus) associated with first trimester exposure to EFV	Routine PhV	None
5. Alteration in EFV blood levels and CYP2B6 genetic polymorphisms.	Routine PhV	None
6. Urolithiasis/Nephrolithiasis	Routine PhV	None
7. Malignant Neoplasms	Routine PhV	None
8. Exacerbation of Sustiva-related AEs when switching from oral solution to capsule sprinkle	Routine PhV	A Dear Healthcare Provider letter will be distributed to providers treating paediatric HIV patients in the Member States where Sustiva Oral Solution is currently available (i.e., France, Germany, Ireland, Italy, Spain, UK)
9. Use in pediatric populations	Routine PhV	None
10. Use in elderly populations	Routine PhV	None
11. Patients with renal impairment	Routine PhV	None
12. Patients with hepatic impairment	Routine PhV	None
13. Development of neurocognitive changes in HIV-infected children	Routine PhV	None

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.1.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated for Sustiva. Labelling and Package Leaflet has been updated accordingly.

Updates affect the Product Information for Sustiva 50mg, 100mg and 200mg hard capsules and 600mg film-coated tablets. The changes to the product information are presented as new text underlined and deleted text marked as strikethrough.

The SmPC, Labelling and PL of Sustiva 30 mg/ml oral solution was removed as the oral solution will not be marketed anymore.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

4.1 Therapeutic indication

SUSTIVA is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 ~~years~~ months of age and older and weighing at least 3.5 kg.

SUSTIVA has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm^3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing SUSTIVA.

For a summary of clinical and pharmacodynamic information, see section 5.1

4.2 Posology and method of administration

[...]

Dose adjustment

[...]

Children and adolescents (3 months 17 years)

The recommended dose of efavirenz in combination with a PI and/or NRTIs for patients between 3 months and 17 years of age is described in Table 1. Efavirenz intact hard capsules must only be administered to children who are able to reliably swallow hard capsules.

Table 1:
Paediatric dose to be administered once daily*

Body Weight **kg**	**efavirenz** **Dose (mg)**	**Number of Capsules or Tablets and Strength to Administer**
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
~~13~~ 7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

*For information on the bioavailability of the capsule contents mixed with food vehicles, see section 5.2.

Special populations

[...]

Paediatric population

The safety and efficacy of efavirenz in children below the age of 3 ~~years~~ months or weighing less than ~~13~~ 3.5kg have not ~~yet~~ been established. ~~Currently~~ No data are available ~~data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.~~

Method of administration

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse reactions (see sections 4.4. and 5.2).

~~*Alternative method of administration*~~
Patients who cannot swallow

~~For children~~ Capsule sprinkle: for patients at least 3 ~~years~~ months old and weighing at least ~~13 kg and adults~~ 3.5 kg who cannot ~~reliably~~ swallow ~~hard~~ capsules, ~~efavirenz solution is the preferred formulation. Administration of~~ the capsule contents can be administered with a small amount ~~(1-2 teaspoons) of food may be considered for patients who cannot tolerate the oral solution~~ of food using the capsule sprinkle method of administration (see section 6.6 for instructions). No additional food should be consumed for up to 2 hours after administration of efavirenz. ~~There are limited safety and tolerability data for administration of the capsule contents in paediatric patients.~~

4.4 Special warnings and precautions for use

[...]

Seizures

Convulsions have been observed in adult and paediatric patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

[...]

Paediatric population

Efavirenz has not been evaluated in children below 3 ~~years~~ months of age or who weigh less than ~~13~~ 3.5 kg. Therefore, efavirenz should not be given to children less than 3 ~~years~~ months of age.

Rash was reported in~~26 of 59~~ 59 of 182 children (~~46~~32%) treated with efavirenz ~~during a 48 weeks period~~ and was severe in ~~three~~ six patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ~~Individuals with these conditions may take efavirenz oral solution, which is free from lactose.~~

4.8 Undesirable effects

[...]

Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (~~in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46%~~ 59 of 182 (32%) treated with efavirenz) and was more often of higher grade than in adults (severe rash was reported in ~~5.3%~~ 6 of 182 (3.3%) of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. ~~Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5% of patients~~

~~experienced nervous system symptoms of moderate intensity, predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms.~~

5. Pharmacological properties

5.1 Pharmacodynamics properties

[…]

Paediatric population

~~ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/ml at 48 weeks was 60% (95%, C.I. 47, 72), and 53% (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/ml. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm^3 from baseline. The durability of the response was similar to that seen in adult patients.~~

Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in antiretroviral-naive and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with SUSTIVA. At baseline, median plasma HIV-1 RNA was 5.88 $\log_{10}$ copies/mL, median CD4+ cell count was 1144 cells/mm^3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm^3 and the median increase in CD4+ percentage was 6%.

Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with SUSTIVA. At baseline, median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL, median CD4+ cell count was 367 cells/mm^3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm^3 and the median increase in CD4+ percentage was 13%.

Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of SUSTIVA in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with SUSTIVA. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 $\log_{10}$ copies/mL, median CD4+ cell count was 755 cells/mm^3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm^3 and the median increase in CD4+ percentage was 5%.

5.2 Pharmacokinetic properties

[…]

Paediatric population

~~In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state C_{max} was 14.1 µM, steady state C_{min} was 5.6 µM, and AUC was 216 µM·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.~~

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 5 by weight ranges that correspond to the recommended doses.

Table 5: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ µM·h	Mean C_{max} µg/mL	Mean C_{min} µg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

6.6 Special precautions for disposal and other handling

[…]

For ~~children~~ patients at least 3 ~~years~~ months old and weighing at least ~~13 Kg and adults~~ 3.5 kg who cannot ~~reliably~~ swallow ~~hard~~ capsules, ~~efavirenz oral solution is the preferred formulation. Administration of~~ the capsule contents can be administered with a small amount (1-2 teaspoons) of food ~~may be considered for patients who cannot tolerate the oral solution. In a palatability study in healthy adults of efavirenz mixed with applesauce, grape jelly, yogurt, or infant formula, grape jelly received the highest rating of good overall taste~~ using the capsule sprinkle method of administration. Patients and caregivers must be instructed to open the capsule ~~vertically~~ carefully to avoid spillage or dispersion of the capsule contents into the air. It is recommended to hold the capsule with the cap facing up and to pull the cap away from the body of the capsule, and to mix the capsule contents with food in a small container. The mixture should be administered as soon as possible, but no more than 30 minutes after mixing. After administration of the efavirenz-food mixture, an additional small amount (approximately 2 teaspoons) of food must be added to the empty mixing container, stirred to disperse any remaining residue of the medicinal product, and administered to the patient. No additional food should be consumed for up to 2 hours after administration of efavirenz.

Package leaflet

1. What SUSTIVA is and what it is used for

SUSTIVA, which contains the active substance efavirenz, belongs to a class of antiretroviral medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). It is an **antiretroviral medicine that fights human immunodeficiency virus** (HIV-1) infection by reducing the amount of the virus in blood. It is used by adults, adolescents and children 3 ~~years~~ months of age and older and weighing at least 3.5 kg.
Your doctor has prescribed SUSTIVA for you because you have HIV infection.
SUSTIVA taken in combination with other antiretroviral medicines reduces the amount of the virus in the blood. This will strengthen your immune system and reduce the risk of developing illnesses linked to HIV infection.

2. What you need to know before you take SUSTIVA

[…]

Children and adolescents
SUSTIVA is not recommended for children under the age of 3 ~~years~~ months or weighing less than ~~13~~ 3.5 kg because it has not been adequately studied in these patients.

3. HOW TO TAKE SUSTIVA

[...]

Use in children and adolescents

- SUSTIVA 50 mg hard capsules can be taken by children and adolescents 3~~years~~ months of age and older and weighing at least ~~13~~ 3.5 kg who are able to swallow the capsules. Opening the capsule and taking the contents with a small amount of food may be considered for children who cannot swallow the hard capsule ~~and cannot tolerate the oral solution.~~
- The dose for children ~~weighing 40 kg or more is 600 mg once daily.~~ ☐The dose fo
  ~~less than 40 kg~~ and adolescents is calculated by body weight and is taken once daily as shown below:

Body Weight kg	SUSTIVA Dose (mg)	Number of Capsules or Tablets and Strength to Administer
3.5 to < 5	100	one 100 mg capsule
5 to < 7.5	150	one 100 mg capsule + one 50 mg capsule
~~13~~7.5 to < 15	200	one 200 mg capsule
15 to < 20	250	one 200 mg capsule + one 50 mg capsule
20 to < 25	300	three 100 mg capsules
25 to < 32.5	350	three 100 mg capsules + one 50 mg capsule
32.5 to < 40	400	two 200 mg capsules
≥ 40	600	one 600 mg tablet OR three 200 mg capsules

~~SUSTIVA oral solution is preferred for~~ For children who are not able to swallow the capsules ~~However, if a child does not tolerate the oral solution~~, the doctor may recommend opening the hard capsule and mixing the contents with a small amount (1-2 teaspoons) of food (e.g. ~~applesauce, grape jelly, yogurt or infant formula). In a taste preference study, efavirenz mixed with grape jelly received the highest rating~~ yogurt). The capsules must be opened carefully so that the contents do not spill or escape into the air. Hold the capsule ~~vertically~~ with the cap facing up and pull the cap away from the body of the capsule. Use a small container for mixing. Give the mixture to the child as soon as possible, but no more than 30 minutes after mixing. Make sure the child eats the full amount of the mixture of food and capsule contents. Add another small amount (approximately 2 teaspoons) of the food to the empty mixing container, stirring to make sure there is no ~~medicine~~ drug residue remaining in the container, and have the child eat the full amount again. The child should not be given any additional food for 2 hours. The doctor may also recommend this method of taking ~~SUSTIVA~~ Sustiva for adults who cannot swallow capsules ~~and do not tolerate the oral solution.~~

Instructions of the capsules sprinkle methods were introduced in the Package leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH. The CHMP considered it unacceptable it was not in line with article 59(3) of Directive 2001/83/EC where is stated that the PL shall reflect the results of consultations with target patients groups to ensure that it is legible, clear and easy to use.

Therefore, the CHMP recommended to perform a user test consultation and to submit the report within 3 months after the EC decisions of this procedure.

This report will include the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Provided that amendments to the PL are proposed as a result of the user test, these could be submitted as a 61(3) Notification (i.e. Article 61(3) refering to Directive 2001/83/EC).

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efavirenz, in combination with 2 NRTIs is currently the preferred NNRTI for initial therapy of children ≥3 years of age based on clinical trial experience in children. There is a need of efavirenz therapy in children below the age of 3 years as all children have to start ARV therapy once diagnosis of HIV infection is confirmed. In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV (EMEA/CPMP/EWP/633/02, Rev 3) based on the identification of suitable dose regimens and the expectation that PK/PD relationship are the same in children as in adults, an extrapolation of efficacy data obtained in adults to children may be accepted.

The efficacy and safety profile of efavirenz has already been largely proven in the initial application and throughout over 10 years of post-marketing experience in patients > 3 years.

Furthermore, the specific safety profile observed with the sprinkled capsule method in the target population along with data from the adult study AI266095 provided sufficient reassurance to conclude that does not differ from the one already well known for efavirenz.

Capsule sprinkled dosing method consistently showed less intra and inter-individual variability, along with higher bioavailability relative to oral solution administration. This favours the removal of the oral solution formulation, which has been endorsed by the CHMP.

Uncertainty in the knowledge about the beneficial effects

Limited efficacy and safety data was provided in support of this application. Twenty-four subjects from one single study (AI266922) were the only available data generated in the target population using the sprinkled capsule contents as the method of administration. Comparable data between capsules (either intact or sprinkles) and oral solution was also very limited (only 12 subjects from Study AI266922).

Risks

Unfavourable effects

The overall safety profile did not differ from the one that had been previously assessed, based mostly on the same data, and which is already reflected in the SmPC. No signal indication of a different safety profile was detected in the submitted safety data.

Uncertainty in the knowledge about the unfavourable effects

Safety data in the paediatric population aged 3 months to 3 years was limited to 61 subjects. Formal analyses and comparisons between age groups and treatment groups were limited. However, the small safety dataset did not point to any new or unexpected safety signal or characteristic in the overall population.

The CHMP considered that the specific safety profile of the sprinkled capsule method in children aged 3 months to 3 years was scarce. Furthermore, there was the safety concern related to the expected higher exposure when switching patients from oral solution to the same dose as capsule sprinkle.

Therefore, the CHMP considered necessary the development of a DHPC to ensure closed safety monitoring after switch of patients from Sustiva oral solution to the capsule sprinkle dosing method.

There still an uncertainty of the long term neurocognitive development in children for which future monitoring is warranted.

Benefit-Risk Balance

Three main paediatric studies were submitted in support of this application (Studies PACTG 382, PACTG 1021 and AI266922). These studies had already been satisfactorily assessed by the CHMP as part of the assessment of post-authorisation measures of Sustiva. Therefore, none of the main studies were originally designed to assess the efficacy of EFV administered as the sprinkled capsule contents in the target population.

As stated in the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infections (EMEA/CPMP/EWP/633/02), provided that reliable pharmacokinetic data support robust dose recommendations, an extrapolation of efficacy data obtained in adults to children may be accepted. Based on the submitted PK/PD modelling data, suitable dose regimens were identified and the extrapolation of efficacy data obtained in adults to children was accepted. In addition the efficacy observed in the paediatric studies provided additional reassurance. Similar exposure is assumed to provide similar antiviral response. The target exposure was defined as a median AUC of 190 uM*h to 380 uM*h which corresponds to the observed median and 2xmedian exposure in adult patients treated with 600 mg QD.

The CHMP considered that the PPK model predictive performance was considered acceptable and supportive of the weight-based dosing recommendations.

The CHMP concluded that the benefit/risk balance is favourable for the use of Sustiva in children from 3 months of age to less than 3 years of age and weighing at least 3.5 Kg.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**	**Annex(es) affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I and IIIB
C.I.7.a	C.I.7.a - Deletion of - a pharmaceutical form	IB	I, IIIA, IIIB and A

Extension of indication for the treatment of HIV-1 to include children from 3 months to 3 year of age and weighing at least 3.5kg and removal of the oral solution pharmaceutical form for Sustiva (efavirenz). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, and 6.6 of the Summary of Product Characteristics (SmPC) are updated. The Package Leaflet is updated accordingly. In addition, the SmPC, Labelling and Package Leaflet of the 30 mg/ml oral solution is deleted.

The requested group of variations proposed amendments to the Annex A, SmPC, Labelling and Package Leaflet.