CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number	201-152/S-004 (b) (4)
Submission Code	SE-5
Priority or Standard	Standard
Submit Date	August 29, 2011
Received Date	August 29, 2011
PDUFA Goal Date	November 11, 2012
Division / Office	Division of Antiviral Products/ Office of Antimicrobial Products
Reviewer Name	Andreas Pikis, M.D.
Review Completion Date	November 2, 2012
Established Name	Nevirapine extended-release
Trade Name	Viramune XR
Therapeutic Class	Antiretroviral (non-nucleoside reverse transcriptase)
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Formulation	Tablet (100, 400 mg)
Dosing Regimen	Once daily (dose based on body surface area)
Indication	Treatment of HIV-1 infection (b) (4)

This review amends the Clinical review for supplemental NDA (sNDA) 201-152/S-004 submitted to this NDA on May 25, 2012.

Of note, sNDA 201-152/S-004 (b) (4) sNDA 201-152/S-004 for the indication of nevirapine extended-release (NVP XR) tablets, in combination with other antiretroviral agents, in HIV-1 infected pediatric patients 6 to < 18 years of age, (b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

(b) (4). Of note, the Applicant received a waiver for studies in children < 3 years of age at that time.

After a thorough review and based on the deficiencies noted during the inspection by the Office of Scientific Investigations (OSI) for the bioanalytical portion of Study 1100.1518 at (b) (4), the Division of Antiviral Products (DAVP) decided VIRAMUNE XR (b) (4) A Complete Response Letter outlining the deficiencies needed to be addressed by the Applicant was issued on June 22, 2012. The Applicant was asked to perform statistical analyses on a revised pharmacokinetic dataset taking into consideration the following:

a. Exclude the original and repeat analysis data for all analytical runs containing QCs that failed acceptance criteria according to Agency's "*Guidance for Industry-Bioanalytical Method Validation"* including the following four runs:
    - AY1_100125_QP1_SE
    - AY1_100202_QP1_LM
    - AY1_100118_QP1_LM2
    - AY1_100113_QP2_LM

b. Exclude the repeat analysis data for all samples which passed during initial runs, including the following runs:
    - AY1_100118_QP1_SE2
    - AY1_100115_QP1_SE2
    - QY1_100118_QP1_LM
    - AY1_100121_QP2_LM
    - AY1_100121_QP1_SE
    - QY1_100118_QP1_SE

The Applicant addressed the deficiencies stated in the June 25, 2012, Complete Response Letter by performing statistical analyses based on the revised pharmacokinetic dataset. Based on the review of the following two studies and the Applicant's resubmissions addressing the deficiencies noted by the OSI, the DAVP determined that the submitted data, together with the previous demonstration of efficacy in adult patients, support the approval of NVP XR tablets, in combination with other antiretroviral agents, for the treatment of HIV-1 infected pediatric

patients 6 to < 18 years of age. (b) (4)

Study 1100.1517 was an open-label, non-randomized, single-dose parallel-group study of pharmacokinetic properties of 200 mg (2 x 100 mg tablets once daily) and 300 mg (3 x 100 mg tablets once daily) nevirapine extended release formulation compared to 200 mg VIRAMUNE tablet as well as to 400 mg nevirapine extended release tablet following oral administration in healthy male volunteers. The pharmacokinetic findings of this study confirmed the extended release characteristics of the NVP XR 100 mg tablet. The findings from this study were unaffected by the bioanalytical deficiencies noted by OSI.

Study 1100.1518, (b) (4) was an open-label, multiple-dose, crossover study to evaluate the steady-state pharmacokinetic parameters of NVP XR in HIV-1 infected children, with an optional extension phase. Eighty-five children 3 to < 18 years of age were enrolled in the pharmacokinetic part of Study 1100.1518, and 80 of the 85 children completed this part of the study. However, the revised dataset created to address the deficiencies noted by the OSI contained evaluable intensive pharmacokinetic data for 17 patients only. Patients were treated for at least 18 weeks with a nevirapine immediate-release (NVP IR)-based regimen and had undetectable HIV RNA levels (<50 copies/mL) prior to enrollment. Following screening, qualified children and adolescents received NVP IR based on BSA (150 mg/m^2 twice a day) or body weight (for patients < 8 years of age the dose was 7 mg/kg twice a day; for patients ≥ 8 years of age the recommended dose was 4 mg/kg twice a day) for at least 10 days (lead-in phase) prior to the collection of serial blood samples for pharmacokinetic analysis on study Day 11. On Day 12, patients were switched from NVP IR treatment to NVP XR treatment. NVP XR doses were selected based on the total daily NVP IR dose which patients received on Day 1. All patients received NVP XR for a mean of 10 days prior to the collection of serial blood samples on study Days 21 and 22 for pharmacokinetic analyses. Patients who completed Day 22 could either conclude their participation in the study or enter into the optional extension phase (OEP). Forty of the 85 subjects who entered the initial part of the study were enrolled in the optional extension phase. Thirty-nine of the 40 subjects completed at least 24 weeks of treatment and one subject discontinued prematurely due to an adverse reaction.

Overall, the mean systemic nevirapine exposures in children 6 to less than 18 years of age following administration of NVP XR and NVP IR were similar. The observed geometric mean ratios of NVP XR to NVP IR were approximately 97% for $C_{min,ss}$ and 94% for AUC_{ss} with 90% confidence intervals within 80% - 125%; the ratio for $C_{max,ss}$ was lower and consistent with a once daily extended-release dosage form. Geometric mean steady-state plasma NVP XR pre-dose trough concentrations were 3,743 ng/mL, and 6,556 ng/mL in age groups 6 to < 12 years, and 12 to < 18 years of age, respectively. (b) (4)

All 39 subjects who completed the optional extension phase of the study continued to have undetectable plasma HIV-1 RNA levels (< 50 copies/mL) after 24 weeks of treatment with an NVP XR-based regimen. The median CD4+ cell counts after 24 weeks of treatment for the 3 to < 6 years, 6 to < 12 years, and 12 to < 18 years of age groups, were 1113 cells/mm^3, 853 cells/mm^3, and 682 cells/mm^3, respectively. These CD4+ cell counts were similar to those observed at baseline. The nature of the clinical and laboratory adverse events observed in this study does not raise any new safety concerns.

It is noteworthy that the DAVP and the Pediatric Review Committee determined that the submitted data fulfilled the PREA PMR for children 6 to < 18 years of age. However, the Applicant needs to provide pharmacokinetic data to support a dosing regimen for children 3 to less than 6 years of age.

1.2 Risk Benefit Assessment

The safety profile of nevirapine is well characterized. Adverse events of concern include rash and hepatic toxicity, which usually occur within the first 18 weeks of treatment. Nevirapine was initially marketed as an immediate-release tablet (VIRAMUNE®, 1996) and oral suspension formulation (1998) administered twice daily together with other antiretroviral agents. In 2011, the extended release form of nevirapine administered once daily was approved for adult HIV-1 infected patients. The once daily regimen provides convenience and therefore better adherence, a key factor in the success of treatment for HIV-1 infection.

In studies performed in adults, NVP XR was shown to be effective and safe in treatment-naïve subjects as well as in subjects switched from NVP IR 200 mg twice daily. No serious risks were identified with NVP XR above and beyond to what is already known for NVP IR. (b) (4)

The results of this study demonstrated that in pediatric patients 6 to < 18 years of age the level of exposure to nevirapine was similar to that observed in adults. This study also demonstrated that there was no virologic failure and there were no new safety concerns. In conclusion, the use of NVP XR in pediatric patients 6 to < 18 years of age who can swallow tablets will provide convenience and better adherence with no greater risk for safety or efficacy than with the currently approved immediate-release formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No specific Risk Management Activities were requested from the Applicant.

1.4 Recommendations for Postmarket Requirements and Commitments

These submissions fulfilled the PREA PMR for pediatric patients 6 to ≤ 18 years of age. However, the PREA PMR for children 3 to < 6 years of age is still outstanding. No additional post-marketing commitments were requested from the Applicant.

2 Introduction and Regulatory Background

2.1 Product Information

Nevirapine is the first non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 virus approved in the United States (1996). Nevirapine binds directly to reverse transcriptase and blocks the RNA- and DNA-dependent polymerase activities by causing disruption of the enzyme's catalytic site. Nevirapine was initially marketed as an immediate-release tablet (VIRAMUNE®, 1996) and oral suspension formulation (1998) administered twice daily together with other antiretroviral agents.

It has been shown that adherence, along with the potency of the drug combination, is crucial for the success of treatment against HIV-1 infection. In order to increase adherence to antiretroviral therapy, once daily regimens are now favored by both physicians and patients. As a result, Boehringer Ingelheim developed an extended-release tablet of nevirapine to be administered once daily in adult HIV-1 infected patients (VIRAMUNE XR, 2011). (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment of HIV infection in the pediatric population relies on drugs available from five mechanistic classes namely, nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), NNRTIs, integrase inhibitors, and fusion inhibitors (Table 1). Drugs in the NNRTI class approved for pediatric use include nevirapine immediate-release formulation (approved for children ≥ 15 days of age), efavirenz (approved for children ≥ 3 years of age), and etravirine (approved for children ≥ 6 years of age).

Table 1: Currently approved pediatric antiretroviral drugs

Drug Class	Generic Name	Trade Name	Pediatric Ages Approved
NRTIs	Zidovudine	Retrovir	≥ 6 weeks
	Didanosine	Videx	≥ 15 days
	Stavudine	Zerit	From birth
	Lamivudine	Epivir	≥3 months
	Abacavir	Ziagen	≥3 months
	Tenofovir	Viread	≥ 2 years
	Emtricitabine	Emtriva	From birth
NNRTIs	Nevirapine	Viramune	≥ 15 days
	Efavirenz	Sustiva	≥ 3 years
	Etravirine	Intelence	≥ 6 years
PIs	Ritonavir	Norvir	> 1 month
	Nelfinavir	Viracept	≥ 2 years
	Fosamprenavir	Lexiva	≥ 2 years
	Lopinavir/ritonavir	Kaletra	≥ 14 days
	Atazanavir	Reyataz	≥ 6 years
	Darunavir	Prezista	≥ 3 years
	Tipranavir	Aptivus	≥ 2 years
Integrase Inhibitors	Raltegravir	Isentress	≥ 2 years
Fusion Inhibitors	Enfuvirtide (T-20)	Fuzeon	≥ 6 years

2.3 Availability of Proposed Active Ingredient in the United States

Nevirapine immediate-release is available as tablet (VIRAMUNE tablets) and oral suspension (VIRAMUNE Oral Suspension):

- VIRAMUNE tablets, 200 mg, are white, oval, bioconvex tablets, 9.3 mm x 19.1 mm. One side is embossed with “54 193”, with a single bisect separating the “54” and “193”. The opposite side has a single bisect. They are supplied in bottles of 60 and in unit dose packages of 14.
- VIRAMUNE Oral Suspension is a white to off-white preserved suspension containing 50 mg nevirapine in each 5 mL. VIRAMUNE suspension is supplied in plastic bottles with child-resistant closures containing 240 mL of suspension.

Nevirapine extended-release is available in the United States as a 400 mg yellow, oval bioconvex tablet with “V04” on one side and the Boehringer Ingelheim logo on the other side. VIRAMUNE XR tablets are supplied in bottles of 30.

2.4 Important Safety Issues With Consideration to Related Drugs

The NNRTI class comprises of four available agents: efavirenz, nevirapine (immediate-release and extended-release), etravirine, and rilpivirine. Delavirdine, an approved NNRTI, is no longer marketed and rilpivirine is not currently approved for children.

Rash, including severe skin or hypersensitivity reactions, is a major safety concern with the use of nevirapine, efavirenz, and etravirine, whereas hepatotoxicity is also a major safety concern with nevirapine and efavirenz. Neuropsychiatric adverse events have been associated with the use of efavirenz and rilpivirine. The risk of any of these events varies with the individual medication. However, the risk of hepatotoxicity and skin disorders appears to be higher with the use of nevirapine and they are contained in the box warning of the package insert.

Another limitation of the NNRTIs is their relatively low genetic barrier to resistance. Resistance to efavirenz, nevirapine, and rilpivirine can arise as the result of a single amino acid substitution in the reverse transcriptase gene. These mutations can often confer cross-resistance within the class. However, etravirine has higher barrier to resistance and it has demonstrated antiviral activity against isolates with mutations conferring resistance to the other NNRTIs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

August 2007: The Applicant proposed the design of the pediatric clinical development plan for NVP XR tablets in the End-of-Phase II briefing package.

September 2007: The DAVP agreed with the Applicant on the following issues:

- Applicant's proposal to develop a 100 mg NVP XR tablet (b) (4)
- Applicant's proposals to conduct a pediatric pharmacokinetic trial, 1100.1518, to study the steady state pharmacokinetics of pediatric doses with this formulation and, by achieving similar exposure levels in children as previously established in adults, to extrapolate the long-term efficacy results from the adult pivotal trial, 1100.1486, to children.
- Applicant's proposal to seek a waiver for studies in children < 3 years of age

September 2009: The Applicant informed the DAVP of a delay in meeting the timeframes for pediatric study 1100.1518.

October 2009: The DAVP recommended separate submissions for the pediatric and adult data in order to avoid delay of the adult NDA submission.

March 2011: NVP XR was approved for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents.

A PREA PMR was issued asking for a multiple-dose pharmacokinetic and safety study of nevirapine extended-release tablets, in combination with other antiretroviral agents, in HIV-infected pediatric patients 3 to < 18 years old.

The Applicant received a waiver for studies in children < 3 years of age.

August 2011: The Applicant submitted sNDA201-152/S-004. This sNDA includes pharmacokinetic, safety, and antiviral activity data from two studies (b) (4) (b) (4); sNDA 201-152/S-004 for the indication of nevirapine extended-release tablets, in combination with other antiretroviral agents, in HIV-1 infected pediatric patients 6 to < 18 years of age (b) (4)

June 2012: Because of deficiencies noted by the OSI, (b) (4) A Complete Response Letter was issued on June 22, 2012. The Applicant was asked to perform statistical analyses on a revised pharmacokinetic dataset taking into consideration the following:

a. Exclude the original and repeat analysis data for all analytical runs containing QCs that failed acceptance criteria according to Agency's "*Guidance for Industry-Bioanalytical Method Validation"* including the following four runs:
   - AY1_100125_QP1_SE
   - AY1_100202_QP1_LM
   - AY1_100118_QP1_LM2
   - AY1_100113_QP2_LM

b. Exclude the repeat analysis data for all samples which passed during initial runs, including the following runs:
   - AY1_100118_QP1_SE2
   - AY1_100115_QP1_SE2
   - QY1_100118_QP1_LM
   - AY1_100121_QP2_LM
   - AY1_100121_QP1_SE

- QY1_100118_QP1_SE

July 2012: Resubmission of summary pharmacokinetic data, including analytical runs which were "accepted by exception" by the Applicant (i.e., runs in which sample concentrations were "bracketed" by acceptable QCs or calibration curves, even though either the low QC samples or the LLOQ or ULOQ samples failed)

(b) (4)

September 2012: Resubmission of complete pharmacokinetic data taking into consideration all comments from OSI and DAVP.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

At the request of the Division of Antiviral Products and the Office of Clinical Pharmacology, the OSI audited a clinical site used in Study 1100.1518 (Botswana Baylor Children Centre of Excellence, Gaborone, Botswana [Center 2601]). The analytical site (b) (4) was also audited. The inspection of the above sites revealed several serious deficiencies. The most important ones are as follows:

Inspection at (b) (4)

- Data from analytical runs: AY1_100125_QP1_SE, AY1_100202_QP1_LM, AY1_100118_QPl_LM2 and AY1_100113_QP2_LM should be rejected due to failure of the QCs.
- The repeat assay data from analytical runs: AY1_100118_QPI_SE2, AY1_100115_QPl_SE2, AY1_10118_QPl_LM, AYl_100121_QP2-LM, AYl_100121_QPl_SE, and AYI_l00118_QP1_SE should not be accepted, and the original assay data for these samples should be included instead, because the original assay runs were rejected improperly.

(b) (4)
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assure the accuracy of the results, the Applicant was asked to revise the pharmacokinetic dataset taking into consideration the deficiencies noted above and perform a new statistical analysis.

As requested by the DAVP, the inspector also reviewed records that were kept at Study site 2601 for HIV RNA levels at Week 0, Week 12, and Week 24 for all subjects who entered the optional extension phase of the study at this study site. The findings were consistent with those provided in the datasets.

The Applicant addressed the deficiencies stated in the June 25th, 2012, Complete Response Letter by repeating the pharmacokinetic analyses based on the revised dataset. The dataset contained within the resubmission was negatively impacted by the removal of concentration data as specified by the Bioanalytrical Guidance (see Section 5.3)

3.2 Compliance with Good Clinical Practices

The Applicant states the studies were conducted according to accepted ethical standards based on the precepts established by the declaration of Helsinki. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards and Informed Consent was obtained from all subjects.

3.3 Financial Disclosures

In compliance with the rule on Financial Disclosure by Clinical Investigators, the Applicant provided financial interest information for all clinical investigators who participated in Study 1100.1518. According to the Applicant, none of the clinical investigators had a proprietary interest in the product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the United States, nevirapine is currently licensed as an immediate-release formulation (VIRAMUNE 200 mg tablets or 50 mg/mL VIRAMUNE Oral Suspension) or as an extended-release formulation (VIRAMUNE XR 400 mg tablets). In this submission, the Applicant seeks approval to market a 100 mg extended-release tablet that has been developed to improve administration options for pediatric patients. (b) (4)

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Tablet 2. Qualitative and quantitative composition of nevirapine extended-release tablets, 100 mg and 400 mg

Name of Ingredient	mg per tablet		Function	Reference to Standards
Nevirapine Anhydrous	100.00	400.00	Drug Substance	Company Standard in accordance with USP
Lactose Monohydrate	(b) (4)			NF/Ph. Eur.
Hypromellose, (b) (4)				USP/Ph. Eur.
Iron Oxide (b) (4)				NF/EU Color Directives***
Magnesium Stearate				NF/Ph. Eur.
(b) (4)				USP/Ph. Eur.
Total Weight	273.5 †	1094 ††		(b) (4)

*** EU Color Directives (b) (4) as amended.

For further details regarding the chemistry and manufacturing of the VIRAMUNE XR 100 mg tablet, please refer to the review by Jeffrey Medwid, the Chemistry reviewer.

4.2 Clinical Microbiology

These sNDAs do not contain any microbiology data. Please refer to the original NDA reviews for background information.

4.3 Preclinical Pharmacology/Toxicology

No new animal pharmacology and toxicology data were submitted with these sNDAs. Please refer to the original NDA reviews for background information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the HIV-1 virus. It binds directly to reverse transcriptase and blocks the RNA- and DNA-dependent polymerase activities by causing disruption of the enzyme's catalytic site.

4.4.2 Pharmacodynamics

Not applicable.

4.4.3 Pharmacokinetics

This submission includes pharmacokinetic data from Studies 1100.1518 and 1100.1517.

Study 1100.1518 is the pivotal pediatric study. This was a an open-label, multiple dose, crossover study to evaluate the steady-state pharmacokinetic parameters of NVP XR tablets in HIV-1 infected children, with an optional extension phase. The pharmacokinetic results of this study are described in Section 5.3 together with the efficacy and safety data.

Study 1100.1517 determined the pharmacokinetic properties of the 100 mg XR tablet in relation to the 400 mg XR and 200 mg IR tablets in healthy adults. Below is a brief summary of this study.

Study 1100.1517

Study 1100.1517 was conducted at a single center in Germany. This was an open-label, non-randomized, single-dose, parallel-group study designed to determine the pharmacokinetic properties of 100 mg XR tablet when administered as 2 x 100 mg and 3 x 100 mg and to estimate the relative bioavailability of these formulations compared to the 200 mg VIRAMUNE tablet as well as the 400 mg VIRAMUNE XR tablet.

Ninety-six healthy adult male subjects who met the inclusion criteria received a single dose of nevirapine as shown in the following table:

Table 3. Treatment groups and dosing in Study 1100.1517.

Test formulation	Subject number	Strength/designation
A	1-24	Nevirapine XR 200 mg (2 x 100 mg)
B	25-48	Nevirapine XR 300 mg (3 x 100 mg)
C	49-72	Nevirapine XR 400 mg
D	73-96	Nevirapine 200 mg (immediate-release tablet)

Plasma samples for pharmacokinetic analysis were obtained 1 hour before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72, 96, and 144 hours after dosing.

Pharmacokinetic results:

The key pharmacokinetic parameters estimated for each treatment group are listed in Table 4. A comparison of the dose-normalized $AUC_{0-\infty,norm}$ values suggests that NVP exposures were similar between the treatment groups. As expected, administration of the XR formulation resulted in lower $C_{max,norm}$ concentrations (5.50, 5.80, and 5.44 ng/mL/mg for XR 200, 300, and 400 mg, respectively) compared to the IR formulation (10.2 ng/mL/mg). Likewise, longer median T_{max} values were both expected and observed in the XR treatment groups (24.0, 23.9, and 24.0 h for XR 200, 300, and 400 mg, respectively) compared to the IR treatment group (2.01 h).

Table 4. Key pharmacokinetic parameters of nevirapine in Study 1100.1517

		200 mg Nevirapine XR (N=24) Test 1	300 mg Nevirapine XR (N=24) Test 2	200 mg Nevirapine IR (VIRAMUNE®) (N=24) Reference 1	400 mg Nevirapine XR (N=24) Reference 2
$AUC_{0-\infty}$ [ng.h/mL]	Mean	91,800	154,000	105,000	182,000
	CV	33.1	24.9	27.9	24.3
	gMean	72,000	126,000	91,400	152,000
$AUC_{0-\infty,norm}$ [ng.h/mL/mg]	Mean	459	514	524	456
	CV	33.1	24.9	27.9	24.3
	gMean	360	421	457	379
C_{max} [ng/mL]	Mean	1,100	1,740	2,030	2,180
	CV	29.1	19.2	18.9	21.1
	gMean	1,030	1,710	2,000	2,130
$C_{max,norm}$ [ng/ml/mg]	Mean	5.50	5.80	10.2	5.44
	CV	29.1	19.2	18.9	21.1
	gMean	5.17	5.70	9.99	5.32
t_{max}* [h]	Mean	19.6	22.7	2.65	27.4
	CV	34.1	15.0	73.7	23.9
	Median*	24.0	23.9	2.01	24.0
$t_{1/2}$ [h]	Mean	47.7	50.5	41.5	46.2
	CV	24.2	30.7	24.6	29.8
	gMean	46.4	48.3	40.4	44.2
K_a [h^{-1}]	Mean	0.184	0.0975	N/A	0.0556
	CV	215	39.8	N/A	58.4
	gMean	0.105	0.0894	N/A	0.0480

* Median

A relative bioavailability analysis was conducted using dose-normalized exposure data ($C_{max,norm}$ and $AUC_{0-\infty,norm}$) because the doses of test and reference formulations were different for several of the comparisons. Of note, one subject in the NVP XR 200 mg group had significantly lower NVP exposures compared to the rest of the treatment group, and therefore, data generated from this outlier were excluded for subsequent analysis. The results of the analysis are shown in Table 5.

Table 5. Relative bioavailability of NVP XR 200 mg and NVP 300 mg as compared to each of NVP XR 400 mg and NVP IR 200 mg (VIRAMUNE®) with respect to $C_{max,\ norm}$ and $AUC_{0\text{-}inf,\ norm}$*

Comp. T/R Test formulation	Reference 1 XR 400 mg Adj. mean Ratio (Test/ XR400 mg)	90% Conf. int. Lower Limit [%]	Upper Limit [%]	Reference IR 200 mg Adj. mean Ratio (Test/ IR200 mg)	90% Conf. int. Lower Limit [%]	Upper Limit [%]
XR 200 mg						
$C_{max,norm}$	104.6	93.6	116.9	55.7	50.1	61.8
$AUC_{0-\infty,\ norm}$	103.8	91.1	118.2	90.6	79.4	103.4
XR 300 mg						
$C_{max,norm}$	107.2	96.7	118.8	57.0	51.8	62.8
$AUC_{0-\infty,\ norm}$	112.9	100.3	127.1	98.5	87.3	111.2

*One subject in the NVP XR 200 mg was excluded from the analysis because of very low plasma concentrations compared to all other subjects in the treatment group

Based on the dose normalized $AUC_{0-\infty,\ norm,}$ the relative bioavailability of the 100 mg XR tablet was 90.6% (2 x 100 mg XR) and 98.5% (3 x 100 mg XR) compared to IR tablet (200 mg), and was 103.8 % (2 x 100 mg XR) and 112.9% (3 x 100 mg XR) compared to the 400 mg XR tablet.

Conclusions: Overall, the pharmacokinetic findings from Study 1100.1517 confirmed the extended release characteristics of the NVP XR 100 mg tablet.

For more details please see the review by Dr. Leslie Chinn, the Clinical Pharmacology reviewer.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The two clinical studies provided in this submission are summarized in the following table.

Table 6. Studies supporting sNDA 201-152/S-004 (b) (4)

Study No	Objectives of the study	Number of subjects
1100.1517	This was an open-label, non-randomized, single-dose, parallel-group study designed to determine the pharmacokinetic properties of 100 mg XR tablet when administered as 2 x 100 mg and 3 x 100 mg and to estimate the relative bioavailability of these formulations compared to the 200 mg VIRAMUNE tablet as well as the 400 mg VIRAMUNE XR tablet.	96
1100.1518	This was a an open-label, multiple dose, crossover study to evaluate the steady-state pharmacokinetic parameters of NVP XR tablets in HIV-1 infected children, with an optional extension phase.	Pharmacokinetic part of the study: 85 Optional extension phase: 40

5.2 Review Strategy

Trial 1100.1518, the pivotal pediatric study, is the focus of this clinical review. The Applicant's conclusions regarding safety and antiviral activity were confirmed by independent analyses of the data.

The clinical review is focused on the safety, antiviral activity, and pharmacokinetic data from study 1100.1518. The Medical Officer reviewed study design, subject demographics, efficacy results, adverse events, and laboratory abnormalities. The safety data were evaluated either with the use of JMP Statistical Discovery software or the JReview software.

Overview of materials consulted in review: The safety, efficacy, and pharmacokinetic data were submitted electronically following the common technical document format.

Please refer to Dr. Leslie Chinn's clinical pharmacology review for more detailed information on the pharmacokinetic data submitted with this sNDA. Please also refer to Dr. Susan Zhou's statistical review for more detailed information on the efficacy data submitted with this sNDA.

5.3 Discussion of Individual Studies/Clinical Trials

Study 1100.1518
This was a an open-label, multiple dose, crossover study to evaluate the steady-state pharmacokinetic parameters of NVP XR tablets in HIV-1 infected children, with an optional extension phase. The two parts of the study, the pharmacokinetic part and the optional extension phase are described below separately.

Study 1100.1518 – Pharmacokinetic part of the study

This was a an open-label, multiple-dose, crossover study to evaluate the steady-state pharmacokinetic parameters of NVP XR tablets in HIV-1 infected children 3 to < 18 years of age.

Study objectives:

- The primary objective of the study was to determine the pharmacokinetic profile at steady–state of nevirapine XR in children 3 to < 18 years of age.

Primary endpoint:

- trough drug concentration ($C_{pre,N}$)

Secondary endpoints:

- pharmacokinetics: $AUC_{tau,ss}$; $C_{min,ss}$; $C_{max,ss}$; $C_{max,ss}/C_{min,ss}$ ratio; percentage peak-trough fluctuation (PTF); $t_{max,ss}$; CL/F_{ss}; C_{avg}
- safety and tolerability
- efficacy (proportion of patients maintaining viral load <50 copies/mL at Day 22; proportion of patients maintaining viral load <400 copies/mL at Day 22; change in mean CD4+ cell count from baseline at Day 22

Study design:

Eighty-five HIV-1 infected children 3 to < 18 years of age were enrolled in the pharmacokinetic part of the study and 80 of the 85 children completed this part of the study (Botswana-56, South Africa-11, Germany-11, and USA-2 subjects). Patients were to have been treated for at least 18 weeks with a NVP IR-based regimen and have undetectable HIV RNA levels (<50 copies/mL) prior to enrollment (screening). Following screening, qualified children and adolescents were stratified into three groups according to age (3 to < 6 years, 6 to < 12 years, and 12 to < 18 years). Subjects received NVP IR for at least 10 days (lead-in phase). Blood and/or saliva samples were collected to measure pre-dose nevirapine concentrations (C_{trough}) from all subjects on Days 1 and 11; a subset of subjects had samples collected for a 12-hour NVP concentration-time pharmacokinetic analysis on study Day 11. The NVP IR dose was based on body surface area (BSA) or Body Weight (BW) according to the following calculations:

- By BSA: 150 mg/m^2 twice a day
- By BW: For patients < 8 years of age the dose was 7 mg/kg twice a day. For patients ≥ 8 years of age the recommended dose was 4 mg/kg twice a day.

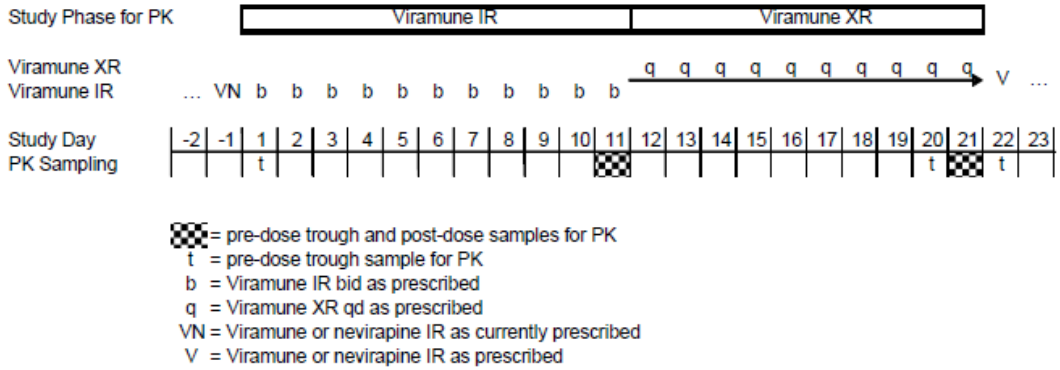
On Day 12 patients were switched from NVP IR treatment to NVP XR treatment. NVP XR doses were selected based on NVP IR dose which patients received on Day 1 (Table 7).

Table 7. Nevirapine XR dose selection

NVP IR dose per day	Viramune XR corresponding dose (once daily)
175 mg to 249 mg/day	200 mg (2 x 100 mg NVP-XR tablet)
250 mg to 349 mg/day	300 mg once (3 x 100 mg NVP-XR tablet)
≥ 350 mg/day	400 mg (1 x 400 mg NVP-XR tablet)

Blood and/or saliva samples were collected to measure pre-dose nevirapine concentrations (C_{trough}) from all subjects on Days 12, 20, 21, and 22; a subset of patients had samples collected for a 12-hour NVP concentration-time pharmacokinetic analysis on study Day 21. All patients received NVP XR for a mean of 10 days. Patients who completed Day 22 could either conclude their participation in the study or enter into the optional extension phase. The trial design is shown in Figure 1.

Figure 1. Study design to compare the steady-state pharmacokinetics of NVP IR and NVP XR formulations



Inclusion criteria:

Patients who met the following inclusion criteria were eligible for participation in this study:

- Signed and dated written informed consent by a parent or legal guardian prior to admission to the study in accordance with good clinical practice and the local laws and regulations. Active assent was given by the patient if the child and/or adolescent were capable of understanding the provided study information based on the local laws and regulations of each country and site.
- HIV-1 infected males or females ≥ 3 and < 18 years old.
- BSA ≥ 0.58 m^2 for patients using BSA to calculate nevirapine IR dose or BW ≥ 12.5 kg for patients using BW to calculate nevirapine IR dose at Screening Visit.
- Treated with a nevirapine IR based regimen for at least 18 weeks prior to Screening Visit (Visit 1); no modifications in the ARV background therapy within the last 2 weeks prior to screening, and expected to stay on the same antiviral regimen for at least 30 weeks.

- An HIV viral load of <50 copies/mL while receiving nevirapine IR, from the last measured VL documented in the medical record obtained within a period of 5 months prior to Screening Visit (Visit 1).
- An HIV viral load of <50 copies/mL at Screening Visit.
- A stable or not decreasing CD4+ cell count according to the Investigator's opinion.
- Acceptable screening laboratory values that indicated adequate baseline organ function according to the Investigator's opinion.
- Alanine aminotransferease (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (ULN) (DAIDS Grade 1).
- Serum creatinine levels ≤ 1.3 x ULN (DAIDS Grade 1).
- Patients able to swallow tablets.

Exclusion criteria:
Patients with any of the following criteria were excluded from the study:
- Any AIDS-related or AIDS-defining illness that was unresolved or not stable on treatment at least 8 weeks prior to Screening Visit.
- Diseases other than HIV infection or conditions that, in the Investigator's opinion, would have interfered with the study.
- Patients who had been diagnosed with malignant disease and who were receiving systemic chemotherapy or were anticipated to receive any therapy during their participation in this trial.
- Use of investigational medications or vaccines within 28 days prior to Screening Visit (Visit 1) or during the trial.
- Use of immunomodulatory drugs within 28 days before Screening Visit (Visit 1) or during the trial (e.g., interferon, cyclosporine, hydroxyurea, interleukin-2).
- Concomitant HIV protease inhibitor (PI) treatment.
- Unwillingness to abstain from ingesting substances during the study which may have altered plasma drug concentrations by interaction with the cytochrome P450 system.
- Female patients of childbearing potential who:
    - had a positive serum pregnancy test at screening,
    - were breast feeding,
    - were planning on becoming pregnant,
    - were not willing to use double-barrier methods of contraception (simultaneous use of two different methods such as diaphragm with spermicidal substance and condom), or required ethinyl estradiol administration. Barrier methods of contraception included diaphragm with spermicidal substance, cervical caps and condoms.

Schedule of assessments:
The schedule of subject monitoring procedures for the pharmacokinetic part of Study 1100.1518 is presented in Table 8.

Table 8. Schedule of assessments and procedures

Flow Chart	Screening	Viramune® PK		Nevirapine XR PK			End of Trial	Post-Trial (PT)[4]
Day	-21 to -14	1	11±2[1]	12[2]	20	21[1]	22	EOT +14 (± 4)
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/EOT**	**PT**
Nevirapine IR	X	X	X				X[5]	
Nevirapine XR (QD)				X	X	X		
Viramune® dispensation and BID dose		X						
Nevirapine XR dispensation				X				
Informed consent	X							
Medical history	X							
Demographic data	X							
X-ray[6]	X							
ECG	X							
HBV, HCV[7]	X							
Urine analysis standard	X							
Urine analysis tox.	X							
Evaluation entry criteria	X	X						
HIV RNA PCR (viral load)	X	X	X				X	X
CD4+ count, percentage	X	X	X				X	X
PK trough (plasma)[8]		X	X			X	X	
PK trough (saliva)[8]			X		X	X		
Post-dose PK sampling (plasma and			X[9]			X[9]		
Chemistry/Hematology[10]	X[11]	X	X			X	X	X
Pregnancy test[12]	X[S]		X[D]				X[S]	X[D]
Physical exam[13]	X[C]	X[T]	X[T]	X[T]	X[T]	X[T]	X[C]	X[C]
AEs, tolerability and CT	X	X	X	X	X	X	X	X
Conclusion trial medication							X	

[1] Patients undergoing post-dose PK sampling on Day 11 and Day 21 will be required to stay overnight if it is considered appropriate by the investigator or local clinical monitor.
[2]Visit 4 must occur the day after Visit 3.
[3]If a patient completes the study, V7/End of Trial (V7/EOT) visit will occur on Day 22. If patient discontinues the study early (early discontinuation [EDC]), V7/EOT visit should occur within one week of the last dose of study medication and PK trough samples will not be required.
[4]Post-trial visit: within 14 days (±4) following last study assessment.
[5]Commercially available nevirapine IR will not be supplied by BI after the EOT.
[6]Any chest X-ray done within the last 12 months prior to screening visit. X-ray is recommended, however if there are any justified objections, it can be omitted.
[7]HBsAg, HBsAb, HBcAb and HCV antibody.
[8]All plasma and saliva PK trough samples (pre-dose, morning samples) will be taken under a fasting period of 4 hours and before the morning dose.
[9]The first 10 patients of each age group will be assigned to post-dose PK sampling on Day 11 (NVP IR, reference treatment) and on Day 21 (NVP XR, test treatment).
[10]For details in hematology and chemistry parameters, see Appendix 16.1.1.1.
[11]Total cholesterol and triglycerides are included in screening lab.
[12]Only required for female patients of childbearing potential. Serum pregnancy test (S) and Urine (dipstick) pregnancy test (D). Additional pregnancy tests will be performed when clinically indicated.
[13]Complete physical examination (C) and targeted physical examination (T): both include vital signs.

Disposition of subjects and baseline characteristics:

A total of 85 subjects (Botswana-60, South Africa-11, Germany-12, and USA-2 subjects) were enrolled in this study. Five subjects discontinued prior to completion of the pharmacokinetic phase for noncompliance and protocol violations (Botswana-4, Germany-1 subject). Intensive

pharmacokinetic sampling was performed on 49 of the 85 subjects: 16 aged 3 to < 6, 16 aged 6 to < 12, and 17 aged 12 to <18 years old).

Table 9. Disposition of patients in the pharmacokinetic part of Study 1100.1518

	3 to <6 yr N (%)	**6 to <12 yr N (%)**	**12 to <18 yr N (%)**	**Total N (%)**
Disposition Through the End of the PK Phase				
Treated	26	26	33	85
Completed at Day 22	25 (96.2)	24 (92.3)	31 (93.9)	80 (94.1)
Discontinued:	1 (3.8)	2 (7.7)	2 (6.1)	5 (5.9)
Non-compliant	0 (0.0)	1 (3.8)	1 (3.0)	2 (2.4)
Other (not related to medication formulation/tolerability)*	1 (3.8)	1 (3.8)	1 (3.0)	3 (3.5)

*One subject entered the study with detectable viral load at screening and was prematurely withdrawn from the study before Visit 3. The exact reason for discontinuation of the other two subjects was not provided.

Patient demographics and baseline characteristics are shown in Tables 10 and 11, respectively.

Table 10. Summary of demographic data of patients enrolled in the pharmacokinetic part of Study 1100.1518

Patient characteristics	**3 to <6 yr N=26**	**6 to <12 yr N=26**	**12 to <18 yr N=33**	**Total N=85**
Sex				
Male	13 (50%)	12 (46%)	13 (39%)	38 (45%)
Female	13 (50%)	14 (54%)	20 (61%)	47 (55%)
Race				
Black	25 (96%)	22 (85%)	32 (97%)	79 (93%)
White	1 (4%)	4 (15%)	1 (3%)	6 (7%)
Hispanic				
Yes	1 (4%)	0 (0%)	0 (0%)	1 (1%)
No	25 (96%)	26 (100%)	33 (100%)	84 (99%)
Country				
Botswana	20 (77%)	16 (62%)	24 (73%)	60 (71%)
South Africa	2 (8%)	4 (15%)	5 (15%)	11 (13%)
Germany	4 (15%)	6 (23%)	2 (6%)	12 (14%)
USA	0 (0%)	0 (0%)	2 (6%)	2 (2%)

Comments: Most of the patients included in the study were from Botswana (71%) and were blacks (93%). The three age groups appear to be balanced.

Table 11. Baseline Characteristics of patients enrolled in the pharmacokinetic part of Study 1100.1518*

	3 to <6 yr N=26	6 to <12 yr N=26	12 to <18 yr N=33	Total N=85
BSA (m^2)				
Mean ± SD	0.7 ± 0.1	0.9 ± 0.2	1.4 ± 0.2	1.0 ± 0.3
Range	0.6 – 0.8	0.7 – 1.4	1.0 – 1.7	0.6 – 1.7
Height (cm)				
Mean ± SD	103.8 ± 7.1	125.8 ± 9.6	157.8 ± 8.4	131.5 ± 24.2
Range	87.0 - 117.0	110.0 – 149.0	139.0 – 176.0	87.0 – 176.0
Weight (kg)				
Mean ± SD	16.0 ± 2.1	25.8 ± 6.6	45.2 ± 9.6	30.3 ± 14.4
Range	13.0 -22.1	17.7 – 47.0	24.0 – 62.2	13.0 – 62.2
CD4+ cell count (cells/mm^3)				
Mean ± SD	1322 ± 392	978 ± 312	715 ± 336	977 ± 425
Range	597 - 2057	495 - 1859	207 - 1567	207 - 2057
CD4+ Cell Count (cells/mm^3) – N(%)				
Missing	1 (4%)	0 (0%)	0 (0%)	1 (1%)
>200 to 350	0 (0%)	0 (0%)	4 (12%)	4 (5%)
>350 to 500	0 (0%)	1 (4%)	5 (15%)	6 (7%)
>500	25 (96%)	25 (96%)	24 (73%)	74 (87%)
CD4+ T cell percentage				
Mean ± SD	39.2 ± 8.7	36.7 ± 7.7	33.1 ± 6.9	36.0 ± 8.0
Range	18.5 – 52.1	21.2 – 48.9	13.4 - 45.6	13.4 – 52.1
CD4+ T cell percentage group – [N(%)]				
Missing	1 (4%)	0 (0.0)	0 (0.0)	1 (1%)
≤15%	0 (0.0)	0 (0.0)	1 (3%)	1 (1%)
>15% to 25%	1 (4%)	2 (8%)	3 (9%)	6 (7%)
>25%	24 (92%)	24 (92%)	29 (88%)	77 (91%)

*One subject in the age group 3 to < 6 years had missing in baseline CD4+ cell count and CD4%.

Comment: More adolescents had CD4+ cell count < 500 cells/mm^3 indicating that HIV disease was more advanced in adolescents compared to younger children.

Zidovudine or stavudine plus lamivudine were the most commonly used background antiretroviral therapies inpatients who entered Study 1100.1518 (87%).

Pharmacokinetic results:

While saliva samples were collected for determination of nevirapine trough concentrations, data from these samples were found to have no contribution to the pharmacokinetic profiles determined from plasma samples; data from saliva samples were therefore not used in the Applicant's or the DAVP's analyses.

The revised pharmacokinetic data were negatively impacted by the removal of data after taking into consideration OSI's and DAVP's comments. Although the pre-dose nevirapine steady-state trough concentrations were within the expected range, there was inadequate number of subjects, in the younger age group (3 to < 6 years of age), to enable accurate assessment of the pharmacokinetics of nevirapine.

A summary of the pre-dose nevirapine steady-state trough concentrations for the immediate-release and extended-release formulations for patients participating in the pharmacokinetic part of Study 1100.1518 after resubmission is shown in Table 12.

Table 12. Summary of pre-dose nevirapine steady-state trough concentrations ($C_{pre,ss}$) for IR and XR formulations by age group after resubmission

Age group (years)	Resubmission						Initial submission NVP XR: NVP IR ratio	Adult NVP XR: NVP IR ratio
	NVP XR		NVP IR		Ratio NVP XR: NVP IR	gCV (%)		
	N	gMean (ng/mL)	N	gMean (ng/mL)				
3 to <6	4	4867	4	5697	85.42	12.0	96.67	82.69
6 to <12	10	3743	13	4359	85.87	26.5	83.53	
12 to <18	5	6556	6	5572	117.66	24.0	91.19	

Comments: The average steady-state trough concentrations of the NVP XR were similar to those of NVP IR using the dosing regimen specified in the labeling and similar to those observed in adults.

Removal of the samples as requested by the DAVP did not have a significant impact on NVP steady-state trough concentrations after administration of NVP XR or NVP IR.

Based on the adult studies, maintenance of steady-state concentrations above 3000 ng/mL is crucial for achieving or sustaining viral suppression. The pharmacokinetic data obtained in Study 1100.1518 showed that the mean steady-state plasma NVP trough concentrations ($C_{pre,ss}$) after administration of NVP XR were greater than the minimum NVP plasma concentrations considered necessary for efficacy in subjects across the age range studied (3 to <18 years old).

Based on the above data, the Applicant selected the BSA categories for XR by halving the BSA categories below and above the corresponding IR dose (Figure 2). For example, the BSA for 300 mg XR includes the upper half of IR 250 mg, all of 300 mg, and the lower half of 350 mg.

Figure 2. Proposed nevirapine XR pediatric dosing based on BSA

The Applicant did not calculate exposure (AUC, C_{max}) by age group in the resubmitted dataset. Because the pharmacokinetics of NVP (in particular, parameters related to exposure) are pivotal to approval of the pediatric indication, the number of subjects in each age group with meaningful concentration data (i.e., at least 75% of points on the concentration-time profile for either formulation, which we believe would provide enough information towards an estimate of exposure) were calculated (Table 13). Note that the Applicant felt that there were insufficient concentration data in the resubmitted dataset from two of the subjects included in Table 13 (one in the 6 to <12 year old group following administration of NVP XR and the other in the 12 to <18 year old group following administration of NVP IR) and therefore excluded them from the pharmacokinetic analysis.

Table 13. Numbers of subjects with Viramune® IR and XR plasma concentrations in the initial analysis and after resubmission.

Age group (years)	Initial submission		Resubmission	
	NVP IR (N)	NVP XR (N)	NVP IR (N)	NVP XR (N)
3 to <6	16	16	5	3
6 to <12	16	15	11	11
12 to <18	17	14	5	3

Source: L. Chinn, Clinical Pharmacology reviewer

Comments: The number of subjects in the 6 to <12 years age group is sufficient to account for pharmacokinetic variability (N=11 in both the IR and XR treatment groups) and the relative bioavailability of NVP XR: IR was similar to that of adults. These findings support the approval of NVP XR in patients 6 to <12 years of age.

(b) (4)

Although the number of subjects in the 12 to < 18 year age group is small (b) (4) , the review team decided that these pharmacokinetic data support approval for this age group. This decision was based on DAVP's experience that drugs administered to adolescents provide similar exposure to that in adults, and on a unanimous statement made recently by the Clinical Pharmacology Advisory Committee (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM306989.pdf) that doses for adolescents may be derived using adult data without the need for a pharmacokinetic study.

For more details for the Pharmacokinetic part of Study 1100.1518 please see the review by Dr. Leslie Chinn, the Clinical Pharmacology reviewer.

(b) (4)

(b) (4)

[redacted]

Safety results during the pharmacokinetic part of Study 1100.1518:

A total of 85 subjects were entered and received at least one dose of NVP IR. All these subjects were included in the safety analysis. Although subjects included in the study had received nevirapine IR prior to study for at least 18 weeks prior to study initiation, the start of treatment was considered when they entered the nevirapine IR run-in phase. Therefore, the adverse event reporting period for the NVP IR phase starts from the first run-in phase intake until the first NVP XR intake (duration of exposure about 11 days). The adverse event reporting period for the NVP XR phase starts from the first NVP XR intake until 14 days after the last NVP XR intake.

Adverse events: The following table summarizes the frequency of patients with treatment emergent adverse events ≥ 5% during the NVP IR run-in phase and NVP XR phase during the pharmacokinetic part of the study.

Table 15. Frequency of patients with any AEs ≥ 5% by onset during the pharmacokinetic part of Study 1100.1518 (NVP IR run-in and NVP XR phase)

System organ class/ Preferred term	NVP IR run-in phase N (%)	NVP XR N (%)
Number of patients	85 (100.0)	83 (100.0)
Total with adverse events	24 (28.2)	39 (47.0)
Infections and infestations	8 (9.4)	20 (24.1)
Upper respiratory tract	6 (7.1)	4 (4.8)
Nervous system disorders	6 (7.1)	4 (4.8)
Headache	5 (5.9)	4 (4.8)
Respiratory, disorders	9 (10.6)	5 (6.0)
Cough	7 (8.2)	4 (4.8)
Skin and subcutaneous tissue disorders	5 (5.9)	9 (10.8)
Rash	4 (4.7)	5 (6.0)
General disorders and administration site conditions	3 (3.5)	6 (7.2)

Percentages are calculated using total number of patients per treatment as the denominator.

Comments: There were more subjects with adverse events during the NVP XR phase (47%) compared to the NVP IR phase (28%). This is mainly due to the increased incidence of infections and infestations (9% versus 24% in the NVP IR and NVP XR, respectively). The difference in the frequency of the adverse events might also be influenced by the longer reporting period for the NVP XR period compared to the NVP IR period (31 days vs. 10 days, respectively).

The most frequently reported adverse events for the NVP XR phase by system organ class were infection and infestations followed by skin and subcutaneous tissue disorders and respiratory disorders. However, rash was reported in similar numbers and proportions of subjects in the NVP IR and NVP XR phases.

The frequency of adverse events was similar among the three age groups during the NVP IR and NVP XR phase of the study.

A summary of the adverse events observed during the NVP IR run-in phase and during the NVP XR phase by age group is shown in Table 16 and Table 17, respectively.

Table 16. Summary of adverse events by age group during the NVP run-in phase

	3 to <6 yr	6 to <12 yr	12 to <18 yr	Total
	N (%)	N (%)	N (%)	N (%)
Number of patients	26 (100.0)	26 (100.0)	33 (100.0)	85 (100.0)
Patients with any AE	9 (34.6)	7 (26.9)	8 (24.2)	24 (28.2)
Patients with investigator defined drug-related AEs	4 (15.4)	2 (7.7)	4 (12.1)	10 (11.8)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with DAIDS Grade 1 AEs	9 (34.6)	6 (23.1)	7 (21.2)	22 (25.9)
Patients with DAIDS Grade 2 AEs	0 (0.0)	1 (3.8)	1 (3.0)	2 (2.4)
Patients with DAIDS Grade 3 or 4 AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 17. Summary of adverse events by age group during the NVP XR phase

	3 to <6 yr	6 to <12 yr	12 to <18 yr	Total
	N (%)	N (%)	N (%)	N (%)
Number of patients	25 (100.0)	25 (100.0)	33 (100.0)	83 (100.0)
Patients with any AE	11 (44.0)	14 (56.0)	14 (42.4)	39 (47.0)
Patients with investigator defined drug-related AEs	2 (8.0)	2 (8.0)	6 (18.2)	10 (12.0)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with DAIDS Grade 1 AEs	9 (36.0)	11 (44.0)	10 (30.3)	30 (36.1)
Patients with DAIDS Grade 2 AEs	2 (8.0)	3 (12.0)	3 (9.1)	8 (9.6)
Patients with DAIDS Grade 3 AEs	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.2)
Patients with DAIDS Grade 4 AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with any study drug-related DAIDS Grade 3 or 4 AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

No patient had an adverse event that led to study drug discontinuation. There were no deaths or serious adverse events during the NVP IR or NVP XR phase. Most reported AEs were Grade 1 and 2 (mild or moderate) and only one subject had a DAIDS Grade 3 adverse event (pyrexia) during the NVP XR phase.

Adverse events considered by the investigators to be related to study drug were reported for 10 of the 85 subjects (12%) in the NVP IR phase and 10 of the 83 subjects (12%) in the NVP XR phase of the study. The most common adverse events considered by the investigators to be

possibly drug related were headache (4 of 85 in the NVP IR and 1 of 83 in the NVP XR phase) and rash (2 of 85 in the NVP IR and 4 of 83 in the NVP XR phase).

Of the 10 subjects with adverse events considered to be possibly related to study drug during the NVP XR phase, eight subjects had mild adverse events and two had adverse events of moderate severity (blister 1, and rash 1).

Laboratory abnormalities: There were no clinically important changes in hematology values, bilirubin, creatinine, sodium, and creatinine kinase.

Hepatotoxicity is of major concern with the use of nevirapine and is included in the box warning of the package insert. During the pharmacokinetic part of the study there were no cases with Grades 2, 3, or 4 laboratory abnormalities of total bilirubin. There were no cases with Grades 3 or 4 laboratory abnormalities of transaminases. However, there was one case with Grade 2 ALT values (normal baseline) and one case with Grade 2 AST values (baseline Grade 1).

Several cases had a worsening of amylase levels from baseline. Most of these patients had also abnormal amylase levels at baseline. There was no subject with a worsening of 3 or 4 grades. However, there were 7 subjects with a worsening of 2 grades (5 of the 7 cases had a worsening of 2 grades during the NVP IR period). None of the patients had elevated lipase levels or clinical symptoms of pancreatitis.

Abnormal electrolyte values were rarely observed and were not associated with adverse events.

Study 1100.1518 – Optional extension part of the study

Study 1100.1518 has two parts; the pharmacokinetic part and the optional extension phase. The pharmacokinetic part was a 4-week open-label, non-randomized crossover phase conducted to determine the pharmacokinetic profile of the NVP XR formulation in HIV-1 infected children 3 to < 18 years of age. This part of the study was described above. The second part of the study was an open-label, multiple dose optional extension phase. Patients who completed the first part of the study could either conclude their participation or enter into the optional extension phase.

Study objectives:

The primary objective of the optional extension phase was to evaluate safety, efficacy, and trough concentrations of the NVP XR formulation administered once daily for at least 24 weeks.

Primary endpoints:

The primary endpoint of the 1100.1518 trial was the evaluation of pharmacokinetic parameters at steady-state. This was established during the 4-week pharmacokinetic phase of the study and was reported above.

Secondary endpoints:

All endpoints of the optional extension phase of the study were considered secondary endpoints. These secondary endpoints were:

Efficacy:

- Proportion of patients maintaining a viral load < 50 copies/mL at the time when the last patient completed the Week 24 visit.
- Proportion of patients maintaining a viral load < 400 copies/mL at the time when the last patient completed the Week 24 visit.
- Change in mean CD4+ count (absolute and percentage) from baseline at the time when the last patient completed the Week 24 visit.

Pharmacokinetics:

- $C_{pre,N}$ (trough drug concentration immediately prior to the next scheduled dose)

Safety and tolerability:

- Occurrence of significant changes from baseline laboratory measurements
- Occurrence of adverse events

Study design:
Patients who completed the first part of the study could either conclude their participation or enter into the optional extension phase. Forty of the 80 subjects who completed the pharmacokinetic part of the study were enrolled in the optional extension phase (Botswana-28, Germany-10, USA-2). Subjects from Germany and USA continued directly into the optional extension phase without re-screening. However, in Botswana there was a delay of approximately 8 months in the approval of optional extension phase informed consent form by health authorities. As a result, Botswana subjects were withdrawn from treatment with NVP XR and received NVP IR in the interim period until enrollment in the optional extension phase. After the approval of the informed consent form, subjects interested in participating in the optional extension phase were re-screened to confirm eligibility and eligible subjects were enrolled.

Thirty-nine of the 40 subjects who enrolled in the optional extension phase completed at least 24 weeks of treatment while one subject discontinued prematurely due to an adverse reaction.

Throughout the optional extension phase of the study, NVP XR doses may have been adjusted at any study visit according to patients' body surface area (Table 18) or body weight (Table 19). Safety, efficacy, and trough PK of NVP XR were collected during the study.

Table 18. Dose adjustment algorithm based on BSA

BSA range (m^2)	**Viramune XR tablets dose (mg)**
0.58 – 0.83	200 mg once daily (2 x 100 mg)
0.84 – 1.16	300 mg once daily (3 x 100 mg)
≥ 1.17	400 mg once daily (1 x 400 mg)

Table 19. Dose adjustment algorithm based on BW and age

Patients Weight Range (kg)		**Viramune XR tablets dose (mg)**
< 8 years old	≥ 8 years old	
12.5 to 17.8	17.9 to 31.2	200 mg once daily (2 x 100 mg)
17.9 to 24.9	31.3 to 43.7	300 mg once daily (3 x 100 mg)
25 and above	43.8 and above	400 mg once daily (1 x 400 mg)

Inclusion and exclusion criteria:
Inclusion and exclusion criteria were the same as the criteria for the pharmacokinetic phase.

Schedule of assessments:
The schedule of subject monitoring procedures for the optional extension phase of Study 1100.1518 is presented in Table 20.

Table 20. Schedule of assessments and procedures – optional extension phase

Flow Chart	**Screening**	**Viramune® PK Phase–Run in**		**Nevirapine XR PK Phase**			**Optional Extension Phase (OEP)**					**End of Trial (EOT)[5]**	**Post-Trial[6]**
Week	-3 to -2	1	2		3		4	6	12	18	24	Every 12	EOT	EOT + 4
Day	-21 to -14	1	11±2[1]	12[2]	20	21[1]	22	36± 4	84± 4	126±4	168±4	Every 84±7[4]	EOT	EOT +28 (±7)
Visit	**V1**	**V2**	**V3**	**V4[2]**	**V5**	**V6**	**V7/EOT[3]**	**V8**	**V9**	**V10**	**V11**	**V12-V$_{XX}$[4]**	**OEP/EOT[5]**	**PT**
Viramune® IR	X	X	X										X	
Nevirapine XR (QD)				X	X	X	X	X	X	X	X	X		
Viramune® dispensation and BID dose adjustment		X												
Nevirapine XR dispensation				X			X	X	X	X	X	X		
Informed consent	X						X[7]							
Medical history	X													
Demographic data	X													
X-ray[8]	X													
ECG	X													
HBV, HCV[9]	X													
Urine analysis standard	X													
Urine analysis tox.	X													
Evaluation entry criteria	X	X												
HIV RNA PCR (VL)	X	X	X				X	X	X	X	X	X	X	X
CD4+ count, percentage	X	X	X				X	X	X	X	X	X	X	X
PK trough (plasma)[10]		X	X			X	X	X	X	X	X	X	X	
PK trough (saliva)[10]			X		X	X								
Post-dose PK sampling (plasma and saliva)			X[11]			X[11]								
Chemistry/Hematology[12]	X[13]	X	X			X	X	X	X	X	X	X	X	X
Pregnancy test[14]	X^{S}		X^{D}				X^{S}		X^{D}	X^{D}	X^{D}	X^{D}	X^{S}	X^{D}
Physical exam[15]	X^{C}	X^{T}	X^{T}	X^{T}	X^{T}	X^{T}	X^{C}	X^{T}	X^{T}	X^{T}	X^{T}	X^{T}	X^{C}	X^{C}
AEs, tolerability and CT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conclusion trial medication													X	

[1] Patients undergoing post-dose PK sampling on Day 11 and Day 21 will be required to stay overnight if it is considered appropriate by the investigator or local clinical monitor.
[2]Visit 4 must occur the day after Visit 3.
[3]V7/EOT must be performed for every patient who enters into the OEP.
[4]Visits will continue every 84±7 days until the IND is withdrawn, nevirapine XR becomes approved and is available by prescription in a given country or, the patient enrolls in a compassionate use program.
[5]End of Trial visit during the optional extension phase (OEP/EOT visit) will be performed 12±1 weeks after the last OEP visit. If a patient withdraws from the trial during the OEP early (EDC), OPE/EOT visit should occur within one week of the last dose of study medication and PK trough samples will not be required.

Table 20, continued
[6]Post-trial visit: within 28±7 days following last study assessment.
[7]For participation in the OEP, a new informed consent and assent will be required to be signed by parents or legal guardian and patients (if applicable), respectively.
[8]Any chest X-ray done within the last 12 months prior to screening visit. X-ray is recommended, however if there are any justified objections, it can be omitted.
[9]HBsAg, HBsAb, HBcAb and HCV antibody.
[10]All plasma and saliva PK trough samples (pre-dose, morning samples) will be taken under a fasting period of 4 hours and before the morning dose.
[11]The first 10-12 patients of each age group will be assigned to post-dose PK sampling on Day 11 (NVP IR, reference treatment) and on Day 21 (NVP XR, test treatment).
[12]For details in hematology and chemistry parameters, see Appendix 10.5 of the protocol (Appendix 16.1.1.1).
[13]Total cholesterol and triglycerides are included in screening lab.
[14]Only required for females of childbearing potential. Serum pregnancy test (S) and Urine (dipstick) pregnancy test (D). Additional pregnancy tests will be performed when clinically indicated.
[15]Complete physical examination (C) and targeted physical examination (T): both include vital signs.

Disposition of subjects and baseline characteristics:
A total of 40 out of the 85 subjects who completed the pharmacokinetic part entered the optional extension phase (OEP) of the study.

Patient demographics and baseline characteristics are shown in Table 21 and Table 22, respectively.

Table 21. Summary of demographic data of patients enrolled in the OEP

Patient characteristics	**3 to <6 yr N=12**	**6 to <12 yr N=16**	**12 to <18 yr N=12**	**Total N=40**
Sex				
Male	6 (50%)	8 (50%)	4 (33%)	18 (45%)
Female	6 (50%)	8 (50%)	8 (67%)	22 (55%)
Race				
Black	12 (100%)	12 (75%)	11 (92%)	35 (87.5%)
White	0 (0%)	4 (15%)	1 (8%)	5 (12.5%)
Hispanic				
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No	12 (100%)	16 (100%)	12 (100%)	40 (100%)
Country				
Botswana	9 (77%)	10 (62.5%)	9 (75%)	28 (70%)
Germany	3 (25%)	6 (37.5%)	1 (8%)	10 (25%)
USA	0 (0%)	0 (0%)	2 (17%)	2 (5%)

Table 22. Baseline characteristics of patients enrolled in the OEP

	3 to <6 yr N=12	6 to <12 yr N=16	12 to <18 yr N=12	Total N=40
BSA (m^2)				
Mean ± SD	0.7 ± 0.1	0.9 ± 0.2	1.3 ± 0.2	1.0 ± 0.3
Range	0.6 – 0.8	0.7 – 1.4	1.0 – 1.7	0.6 – 1.7
Height (cm)				
Mean ± SD	105.8 ± 6.9	125.3 ± 10.8	155.3 ± 7.7	128.5 ± 21.4
Range	94.0 - 116.0	110.0 – 149.0	14.0 – 167.0	94.0 – 167.0
Weight (kg)				
Mean ± SD	16.8 ± 2.3	25.4 ± 7.6	40.1 ± 9.3	27.2 ± 11.6
Range	13.7 -22.1	17.7 – 47.0	24.0 – 60.4	13.7 – 60.4
CD4+ cell count (cells/mm^3)				
Mean ± SD	1173 ± 341	905 ± 236	717 ± 436	929 ± 374
Range	605 - 1561	446 - 1496	355 - 1874	355 - 1874
CD4+ Cell Count (cells/mm^3) – N (%)				
>350 to 500	0 (0%)	1 (6%)	4(33%)	5 (12.5%)
>500	12 (100%)	15 (94%)	8 (67%)	35 (87.5%)
CD4+ T cell percentage				
Mean ± SD	31.0 ± 52.2	38.2 ± 6.3	34.5 ± 6.3	37.8 ± 6.3
Range	18.5 – 52.2	27.8 – 47.6	24.0 - 44.3	24.0 – 52.2
CD4+ T cell percentage group – [N(%)]				
>15% to 25%	0 (0%)	0 (0%)	1 (8%)	1 (2.5%)
>25%	12 (100%)	16 (100%)	11 (92%)	39 (97.5%)

Comments: Patient demographics and baseline characteristics were similar to those from the pharmacokinetic part of the study.

Similar to the pharmacokinetic part of the study, zidovudine or stavudine plus lamivudine were the most commonly used background therapies in patients who entered the optional extension phase of the study accounting for 78% of the cases.

Pharmacokinetic results:

Plasma nevirapine trough concentrations: Pre-dose (trough) nevirapine steady-state concentrations during the optional extension phase study Weeks 0, 6, 12, 18, 24, 30, and the combinations of Weeks 24 and 30, in which a large proportion of the 40 patients had NVP trough samples collected, are shown in Table 23. The trough values at entry visit of the optional extension phase (Week 0) are the result of a mixture of mostly NVP IR (Botswana patients who

received interim NVP IR) and a few NVP XR values (from those who continued on NVP XR directly from pharmacokinetic phase of study).

(b) (4)

Comments: Pharmacokinetic results of NVP XR trough concentrations obtained during the optional extension phase were relatively stable and above the 3000 ng/mL threshold. These concentrations were similar to those obtained during the NVP IR and NVP XR phase of the pharmacokinetic part of the study and similar to those obtained from the adult studies.

The pharmacokinetic results obtained during the optional extension phase were also stable when grouped by NVP XR dose (200, 300, or 400 mg QD) or by patient age groups (3 to < 6 years, 6 to < 12 years, and 12 to < 18 years of age) (data not shown).

(b) (4)

(b) (4) .

Safety results:
During the optional extension phase, 37 of the 40 patients (92.5%) reported at least one adverse event. There was one patient with an adverse event judged by the Investigator as drug related (vomiting) and one patient with an adverse event (pulmonary tuberculosis) led to discontinuation of study drug. Among the 37 patients with adverse events, 36 patients reported adverse events that were DAIDS Grade 1, 12 (30.0%) patients reported DAIDS Grade 2 adverse events, and 1 reported DAIDS Grade 3. None of the patients had DAIDS Grade 4 adverse event.

The most frequently reported adverse events were infections and infestations (25 patients, primarily upper respiratory tract infections), and skin and subcutaneous tissue disorders (11 patients, primarily rash). Adverse events reported in 2 or more patients during the optional extension phase are shown in the following table.

Table 24. Adverse events observed in 2 or more patients in an age group during the OEP

	3-<6 yr		6-<12 yr		12-<18 yr		All	
System organ class/Preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients	12	(100.0)	16	(100.0)	12	(100.0)	40	(100.0)
Total with adverse events	12	(100.0)	15	(93.8)	10	(83.3)	37	(92.5)
Infections and infestations	9	(75.0)	11	(68.8)	5	(41.7)	25	(62.5)
Upper respiratory tract infection	3	(25.0)	6	(37.5)	3	(25.0)	12	(30.0)
Nasopharyngitis	0	(0.0)	4	(25.0)	0	(0.0)	4	(10.0)
Rhinitis	3	(25.0)	3	(18.8)	0	(0.0)	6	(15.0)
Pneumonia	2	(16.7)	1	(6.3)	0	(0.0)	3	(7.5)
Bronchitis	1	(8.3)	2	(12.5)	0	(0.0)	3	(7.5)
Metabolism and nutrition disorders	0	(0.0)	2	(12.5)	1	(8.3)	3	(7.5)
Decreased appetite	0	(0.0)	2	(12.5)	0	(0.0)	2	(5.0)
Nervous system disorders	1	(8.3)	0	(0.0)	5	(41.7)	6	(15.0)
Headache	1	(8.3)	0	(0.0)	4	(33.3)	5	(12.5)
Eye disorders	3	(25.0)	4	(25.0)	2	(16.7)	9	(22.5)
Conjunctivitis	3	(25.0)	4	(25.0)	1	(8.3)	8	(20.0)
Respiratory, thoracic and mediastinal disorders	7	(58.3)	10	(62.5)	5	(41.7)	22	(55.0)
Cough	6	(50.0)	9	(56.3)	5	(41.7)	20	(50.0)
Epistaxis	2	(16.7)	0	(0.0)	1	(8.3)	3	(7.5)
Rhinorrhoea	2	(16.7)	0	(0.0)	1	(8.3)	3	(7.5)
Gastrointestinal disorders	2	(16.7)	6	(37.5)	2	(16.7)	10	(25.0)
Vomiting	1	(8.3)	4	(25.0)	0	(0.0)	5	(12.5)
Gastritis	0	(0.0)	1	(6.3)	2	(16.7)	3	(7.5)
Abdominal pain	0	(0.0)	2	(12.5)	0	(0.0)	2	(5.0)
Diarrhoea	0	(0.0)	2	(12.5)	0	(0.0)	2	(5.0)
Skin and subcutaneous tissue disorders	3	(25.0)	3	(18.8)	5	(41.7)	11	(27.5)
Rash	3	(25.0)	2	(12.5)	4	(33.3)	9	(22.5)
General disorders and administration site conditions	3	(25.0)	2	(12.5)	1	(8.3)	6	(15.0)
Pyrexia	3	(25.0)	1	(6.3)	1	(8.3)	5	(12.5)
Injury, poisoning and procedural complications	1	(8.3)	4	(25.0)	0	(0.0)	5	(12.5)
Concussion	0	(0.0)	2	(12.5)	0	(0.0)	2	(5.0)

Deaths: No deaths were reported during the optional extension phase of Study 1100.1518.

Serious adverse events: There was only one patient who experienced a serious adverse event during the optional extension phase. This was a 7-year-old boy who was hospitalized for

concussion after a fall. The patient recovered without treatment and continued study drug. This patient was also hospitalized for an elective tonsillectomy. These serious adverse events were considered not related to study drug.

Serious adverse events related to study drugs: None

Withdrawals due to adverse events: There was one patient who discontinued the study due to an adverse event. This was a 4-year-old boy who discontinued from the study due to pulmonary tuberculosis of moderate severity (DAIDS Grade 2). The patient required treatment with rifampin which cannot be given concomitantly with nevirapine.

Adverse events of concern: Occurrence of rash during the optional extension phase
Nine patients experienced rashes. In eight of the subjects, rashes were mild (DAIDS Grade 1), and in one subject rash was of moderate severity (DAIDS Grade 2). This was a 5-year-old girl who experienced a moderate exanthema on Day 151 of treatment. She recovered in 4 days and continued with study drug. None of the 9 subjects with rash had abnormal transaminases and all cases were not considered related to study drug.

Laboratory abnormalities: There were no clinically important changes in hematology values, bilirubin, creatinine, lipids or lipase levels.

Worsening of 2 grades: There were 3 cases of worsening of 2 grades in amylase levels and 1 case of worsening of 2 grades in ALT levels.

> *Elevated amylase levels:* All 3 cases with a worsening of 2 grades in amylase levels had normal lipase levels and no clinical signs of pancreatitis.
>
> *Elevated transaminase levels:* There were no patients with Grade 3 or Grade 4 transaminase levels. There was one patient with worsening of 2 grades of ALT levels (Grade 2 from Grade 0 at baseline).

Abnormal electrolyte values were rarely observed and were not associated with adverse events.

Conclusions regarding safety and efficacy during the OEP:
Patients enrolled in the optional extension phase of Study 1100.1518 (b) (4) (b) (4) no new safety concerns were identified during this phase. (b) (4)

6 Overall Assessment

6.1 Conclusions

Pediatric use information for many of the approved drugs, including antiviral drugs against HIV, is needed. In general, children have fewer therapeutic options than adults due to lack of pediatric formulations and information to guide clinicians in dosing children.

(b) (4)

Of note, the Applicant previously received a waiver for studies in children < 3 years of age.

After the first review cycle for these sNDAs and because of deficiencies noted during the inspection by the Office of Scientific Investigations, (b) (4) A Complete Response Letter outlining the deficiencies needed to be addressed by the Applicant was issued on June 22, 2012. The Applicant was asked to perform statistical analyses on a revised pharmacokinetic dataset taking into consideration the following:

a. Exclude the original and repeat analysis data for all analytical runs containing QCs that failed acceptance criteria according to Agency's "*Guidance for Industry-Bioanalytical Method Validation"* including the following four runs:
   - AY1_100125_QP1_SE
   - AY1_100202_QP1_LM
   - AY1_100118_QP1_LM2
   - AY1_100113_QP2_LM

b. Exclude the repeat analysis data for all samples which passed during initial runs, including the following runs:
   - AY1_100118_QP1_SE2
   - AY1_100115_QP1_SE2
   - QY1_100118_QP1_LM
   - AY1_100121_QP2_LM
   - AY1_100121_QP1_SE
   - QY1_100118_QP1_SE

Based on the review of the two studies and the Applicant's response to address the deficiencies noted by the Office of Scientific Investigations, the DAVP decided the submitted data, together with the previous demonstration of efficacy in adult patients, support the approval of NVP XR tablets, in combination with other antiretroviral agents, for the treatment of HIV-1 infected

pediatric patients 6 to < 18 years of age. (b) (4) . The overall safety profile of NVP XR in children does not raise any new safety concerns.

6.2 Labeling recommendations

The proposed label submitted with this sNDA has been reviewed by all disciplines involved in the review, and has been discussed with the Pediatric Review Committee. Modifications of the proposed label have been discussed with and agreed upon by the Applicant. The major changes in the modified label involve the following sections:

INDICATIONS AND USAGE

This section was changed to add information on the use of VIRAMUNE XR in the treatment of HIV-1 infection in children. The Pediatric Patients subsection reads as follows:

VIRAMUNE XR is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in children 6 to less than 18 years of age [*see Clinical Studies (14.1, 14.2)*].

DOSAGE AND ADMINISTRATION

This section was changed to add information on the dosing of pediatric patients. The pediatric Dosage and Administration subsection reads as follows:

Pediatric Patients
Pediatric patients may be dosed using VIRAMUNE XR 400 mg or 100 mg tablets. VIRAMUNE XR is dosed based on a patient's body surface area (BSA) calculated using the Mosteller formula. All pediatric patients must initiate therapy with immediate-release VIRAMUNE (as 150 mg/m^2 of VIRAMUNE Oral Suspension or as VIRAMUNE tablets), at a dose not to exceed 200 mg per day, administered once daily for the first 14 days. This lead-in period should be used because it has been demonstrated to reduce the frequency of rash. This lead-in period is not required if the patient is already on a regimen of twice daily immediate-release formulation in combination with other antiretroviral agents.

The recommended oral doses of VIRAMUNE XR for pediatric patients 6 to less than 18 years of age based upon their BSA are described in the table below. The total daily dose should not exceed 400 mg for any patient.

Table 1 Recommended VIRAMUNE XR Dosing for Pediatric Patients 6 to less than 18 years of age by BSA after the Lead-in Period with Immediate-Release VIRAMUNE

BSA range (m^2)	VIRAMUNE XR tablets dose (mg)
0.58 - 0.83	200 mg once daily (2 x 100 mg)
0.84 - 1.16	300 mg once daily (3 x 100 mg)
Greater than or equal to 1.17	400 mg once daily (1 x 400 mg)

Mosteller Formula: $BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ x\ Wt\ (kg)}{3600}}$

ADVERSE REACTIONS
The following information was added under the section of Clinical Trial Experience in Pediatric Patients subsection:

Clinical Trial Experience in Pediatric Patients

Adverse reactions were assessed in Trial 1100.1518, an open-label, multiple-dose, non-randomized, cross-over trial to evaluate the safety and steady-state pharmacokinetic parameters of VIRAMUNE XR tablets in HIV-1-infected pediatric subjects 3 to less than 18 years of age. Safety was further examined in an optional extension phase of the trial. Forty subjects who completed the pharmacokinetic part of the trial were treated with VIRAMUNE XR once daily in combination with other antiretrovirals for a median duration of 33 weeks. The most frequently reported adverse reactions related to VIRAMUNE XR in pediatric subjects were similar to those observed in adults. In pediatric subjects the incidence of Grade 2 or higher drug-related rash was 1%. There were no adverse reactions of Grade 2 or above which were considered to be related to treatment by the investigator that occurred in more than 1% of subjects [*see Use in Specific Populations (8.4), Clinical Pharmacology (12.3), and Clinical Studies (14.2)*].

USE IN SPECIFIC POPULATIONS

The following information was added under the subsection of Pediatric Use:

Pediatric Use
VIRAMUNE XR is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in children 6 to less than 18 years of age [*see Indications and Usage (1), Dosage and Administration (2.3)*].

The use of VIRAMUNE XR for the treatment of HIV-1 infection in pediatric patients 6 to less than 18 years of age is based on pharmacokinetic, safety, and antiviral activity data from an open-label trial with VIRAMUNE XR (b) (4) The results of this trial were supported

by previous demonstration of efficacy in adult patients [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3), and Clinical Studies (14.2)*].

VIRAMUNE XR is not recommended for children less than 6 years of age. Trial 1100.1518 did not provide sufficient pharmacokinetic data for children 3 to less than 6 years of age to support the use of VIRAMUNE XR in this age group. Furthermore, VIRAMUNE XR is not recommended for children less than 3 years of age because they are not able to swallow tablets.

CLINICAL PHARMACOLOGY
The following information was added under the subsection of Pharmacokinetics:

Pediatric Patients
The pharmacokinetics of VIRAMUNE XR were assessed in HIV-1 infected children 3 to less than 18 years of age. Children enrolled received weight or body surface area dose-adjusted immediate-release VIRAMUNE in combination with other antiretrovirals for a minimum of 18 weeks and then were switched to VIRAMUNE XR tablets in combination with other antiretrovirals for 10 days, after which steady-state pharmacokinetic parameters were determined.

Overall, the mean systemic nevirapine exposures in children 6 to less than 18 years of age following administration of VIRAMUNE XR and immediate-release VIRAMUNE were similar. Based on intensive PK data (N=17), the observed geometric mean ratios of VIRAMUNE XR to immediate-release VIRAMUNE were approximately 97% for $C_{min,ss}$ and 94% for AUC_{ss} with 90% confidence intervals within 80% - 125%; the ratio for $C_{max,ss}$ was lower and consistent with a once daily extended-release dosage form.

Trial 1100.1518 did not provide sufficient pharmacokinetic data for children 3 to less than 6 years of age to support the use of VIRAMUNE XR in this age group.

CLINICAL STUDIES

The following information was added under the subsection Pediatric Patients:

Pediatric Patients
Trial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial performed in 85 HIV-1 infected pediatric subjects 3 to less than 18 years of age who had received at least 18 weeks of immediate-release VIRAMUNE and had plasma HIV-1 RNA less than 50 copies per mL prior to trial enrollment. Subjects were stratified according to age (3 to less than 6 years, 6 to less than 12 years, and 12 to less than 18 years). Following a 10-day period with immediate-release VIRAMUNE, subjects were treated with VIRAMUNE XR tablets once daily in combination with other antiretrovirals for 10 days, after which steady-state pharmacokinetic parameters were determined in a subset of patients. Forty of the 80 subjects who completed the initial part of the study were enrolled in an optional extension phase of the trial which evaluated

the safety and antiviral activity of VIRAMUNE XR through a minimum of 24 weeks of treatment. Zidovudine or stavudine plus lamivudine were the most commonly used background therapies in subjects who entered the optional extension phase.

Baseline demographics included: 55% of the subjects were female, 93% were black, 7% were white, and approximately 84% were from Africa. Subjects had a median baseline $CD4^+$ cell count of 925 cells/mm^3 (range 207 to 2057 cells/mm^3).

Of the 40 subjects who entered the treatment extension phase, 39 completed at least 24 weeks of treatment and one subject discontinued prematurely due to an adverse reaction. After 24 weeks or more of treatment with VIRAMUNE XR, all 39 subjects continued to have plasma HIV-1 RNA less than 50 copies per mL. Median $CD4^+$ cell counts for the 3 to less than 6 year, 6 to less than 12 year, and 12 to less than 18 year age groups were 1113 cells/mm^3, 853 cells/mm^3, and 682 cells/mm^3, respectively. These $CD4^+$ cell counts were similar to those observed at baseline.

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

/s/

ANDREAS PIKIS
11/08/2012

MARY E SINGER
11/08/2012
I concur with Dr. Pikis' conclusions and recommendations