U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 201-152/S-004
Drug Name:	Viramune® XR™ (nevirapine) extended-release tablets
Indication(s):	Treatment of HIV-1 infection in pediatric patients
Applicant:	Boehringer Ingelheim, Inc.
Date(s):	Date of submission: August 29, 2011
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Review Priority:	Standard
Biometrics Division:	DB4/OB/OTS/CDER
Statistical Reviewer:	Susan Zhou, Ph.D.
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Key Words: Pediatric Studies, non-randomized trials, descriptive statistics, time window

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1. EXECUTIVE SUMMARY

Boehringer Ingelheim (BI) submitted a pivotal pediatric study 1100.1518 and two single-dose PK studies 1100.1517 and 1100.1531 for the pediatric extended release VIRAMUNE (NVP XR) tablet formulations (b) (4)

(b) (4)

This reviewer focuses on the efficacy evaluation of 1100.1518, consisting of a PK phase and an optional extension phase (OEP). Patients treated with at least 18 weeks of NVP IR-containing regimens prior to entry were stratified to 3 age groups (3-<6 years, 6-<12 years, and 12<18 years) during the PK phase and remained within that stratification during the OEP. The primary objective of 1100.1518 was to establish the PK profile at steady state of NVP XR in children. Efficacy endpoints were considered as secondary, and were originally defined as 1)Proportion of patients maintaining a HIV-1 RNA Viral Load (VL) <50 copies/mL at the end of the PK phase and at the time the last patient reached Week 24 of treatment in the OEP; 2)Proportion of patients maintaining a HIV-1 RNA Viral Load (VL) <400 copies/mL at the end of the PK phase and at the time the last patient reached Week 24 of treatment in the OEP; and 3) Change in mean CD4+ cell count (absolute and T-cell percentage) from baseline at the end of the PK phase and at the time the last patient reached Week 24 of treatment. The study population in the OEP consists of 28 patients from Botswana and 12 from Germany or USA.

It appears that the evaluation of efficacy "at the time the last patient reached Week 24 of treatment" should be modified due to a time delay between the PK phase and OEP for the Botswanan patients. This reviewer conducted sensitivity analyses of these efficacy endpoints at OEP Week 24, and the sponsor used the information at last available visit patients from US and Germany at the time the last patient from Botswana reached Week 24 of treatment.

(b) (4)

2. INTRODUCTION

2.1 Overview

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. On March 25, 2011, BI received the first regulatory approval in the US for VIRAMUNE® Extended Release tablet (NVP XR) use in adults [NDA 201-152]. The NVP XR is administered as a once daily 400 mg regimen. The 200 mg VIRAMUNE® Immediate Release tablet (VIRAMUNE IR, NVP IR) was approved in combination with other ARV agents for the treatment of HIV-1 infection in 1996. The NVP IR is administered as one 200 mg tablet for the first 14 days, followed by one 200 mg tablet twice daily or 150 mg/m^2 once daily for 14 days followed by 150 mg/m2 twice daily thereafter.

In this submission, BI provided the data for a pivotal pediatric study 1100.1518 and two single-dose PK studies 1100.1517 and 1100.1531 for the pediatric NVP XR 100 mg tablet formulation (b) (4)

Study 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial in HIV-1 infected pediatric subjects 3 to < 18 years of age who have received at least 18 weeks of immediate release VIRAMUNE and had HIV-1 RNA <50 copies/mL prior to trial enrollment. Patients were treated with 3 different doses of NVP XR (200 mg, 300 mg and 400 mg) for up to 10 days. The NVP XR dose was assigned based on the NVP IR daily dose taken prior to study entry based on BW or BSA (300 mg/m^2 per day).

The 1100.1518 consists of two phases: 1) a PK phase: an open-label, multiple dose, non-randomized cross-over phase to establish the steady state PK profile (primary endpoint) in HIV-1-infected children; and 2) an optional extension phase (OEP) to evaluate secondary endpoints of safety, efficacy and trough PK after at least 24 weeks of treatment. Forty patients were enrolled for the OEP after the PK phase (n=85) for the week 24 efficacy and safety evaluations.

PK profiles are primary endpoints. The efficacy endpoints are secondary, including percentage of patients with HIV-1 RNA VL< 50 copies/mL, percentage of patients with HIV-1 RNA VL< 400 copies/mL, change from baseline in CD4+ and CD4% at the time when the last patient reaches Week 24 visit. The efficacy endpoints were summarized for three age groups (3-<6. 6-<12 and 12-<18 years of age). No other subgroup analyses were conducted because of the small sample size in the OEP. However, because of the different durations of exposure to NVP XR during the OEP, results were also presented by the two regions: patients from Botswana and Germany/USA.

The Study 1100.1531 is a single dose PK study in healthy adults. The statistical reviewer focuses on the evaluations of secondary efficacy endpoints for 100.1518.

2.2 Data Sources

NDA 201,152/S004 submissions contain the clinical study report for Studies 1100.1518 and 1100.1531. Protocol, synopsis and summary of clinical efficacy and safety for Study 1100.1518 can be found in '~\m2\27-clin-sum' and ' ~\m5\sce-scs\ appendix.pdf', where '~' denotes \\CDSESUB1\EVSPROD\NDA201152\0035. Figure 1 displays the names of six pdf files.

Name	Size	Type	Date Modified
literature-references.pdf	96 KB	Adobe Acrobat Doc...	8/23/2011 11:21 AM
summary-biopharm.pdf	336 KB	Adobe Acrobat Doc...	8/23/2011 11:21 AM
summary-clin-efficacy.pdf	1,070 KB	Adobe Acrobat Doc...	8/19/2011 4:56 PM
summary-clin-pharm.pdf	394 KB	Adobe Acrobat Doc...	8/19/2011 4:56 PM
summary-clin-safety-publishe...	1,953 KB	Adobe Acrobat Doc...	8/19/2011 4:57 PM
synopses-indiv-studies.pdf	95 KB	Adobe Acrobat Doc...	8/23/2011 11:22 AM

Figure 1: Listing of *.pdf files under Subdirectory '~\m2'

SAS *.xpt files, SAS programs for efficacy and safety analyses for 1100.1518 can be found in the four subdirectories of NDA201152\0035 in the CDER EDR.

The 1100.1518 included two phases: PK phase and an optional extension phase (OEP).

- For the PK phase, five analysis datasets and thirty-six tabulated datasets for Week 4 can be found in '~\m5\datasets\1100-1518-4wk\analysis' and '~\m5\datasets\1100-1518-4wk\tabulations', respectively.
- For the OEP, nine analysis datasets in *.xpt format (with define.pdf) and ten SAS programs for the generation of analysis datasets can be found in '~\m5\datasets\1100-1518-24wk\analysis', and thirty-eight raw files in *.xpt format (with define.pdf) can be found in '~\m5\datasets\1100-1518-24wk\tabulations'.

In addition, six datasets in SDTM format (*.xpt) with define.pdf can be found in '~\m5\datasets\1100-1531\tabulations' for 1100.1531.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Both of the raw data and analysis data sets in *.xpt formats can be converted into SAS datasets. Efficacy parameters can be obtained using the define.pdf files to facilitate the efficacy review. Most of the sponsor's results can be replicated with minor numerical discrepancies. However, this reviewer identified some format problems in the analysis datasets (ADaM). It appears that the results in the report may not be the results using submitted ADaM. In the following, we list four data problems.

1. Same demographic variables such as 'Sex', 'Race', 'Ethnic' and 'Region' were respectively defined as numerical values in the 'adameff.xpt' and character strings in the 'baseco24.xpt'.

2. The key variable 'USUBJID' was formatted with different lengths, '$22.' in the 'adameff.xpt' and '$20.' in other analysis datasets such as 'baseco24.xpt', 'inder24.xpt', etc.

3. The variable 'TRTA' (label: treatment actually received) in 'adameff.xpt' is actually the three baseline age categories (See the SAS list file in Appendix 4.1).

4. The comments for 'EXENDY' in 'define.pdf' was 'Study day of end of treatment relative to the sponsor-defined RFSTDTC'. The correct one should be 'Study day of end of treatment relative to the sponsor-defined RFENDTC'.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial in HIV-1 infected pediatric subjects 3 to < 18 years of age who have received at least 18 weeks of immediate release VIRAMUNE and had HIV-1 RNA <50 copies/mL prior to trial enrollment. Patients were treated with 3 different doses of NVP XR (200 mg, 300 mg and 400 mg) for up to 10 days. The NVP XR dose was assigned based on the NVP IR daily dose taken prior to study entry based on BW or BSA (300 mg/m^2 per day).

The 1100.1518 consists of two phases: 1) an open-label, multiple dose, non-randomized cross-over phase to establish the steady state PK profile (primary endpoint) in HIV-1-infected children;

and 2) an optional extension phase (OEP) to evaluate secondary endpoints of safety, efficacy and trough PK after at least 24 weeks of treatment.

The primary endpoints of 1100.1518 were the PK parameters at steady-state during the PK phase. Efficacy endpoints were secondary, including the following:

- Proportion of patients maintaining a VL < 50 at the time when the last patient reaches Week 24 visit.
- Proportion of patients maintaining a VL < 400 at the time when the last patient reaches Week 24 visit.
- Mean change from baseline in CD4 count (absolute and percentage) at the time when the last patient reaches Week 24 visit.

The evaluations of efficacy endpoints "at the time the last patient reached Week 24 of treatment" may not be reasonable due to a median of approximately ten months gap between the PK phase and OEP for the Botswanan patients. To resolve this problem, the sponsor used the corresponding information at last available visit patients from US and Germany at the time the last patient from Botswana reached Week 24 of treatment. This reviewer conducted sensitivity analyses of these efficacy endpoints at OEP Week 24.

3.2.2 Statistical Methodologies

Summary statistics such as sample size, mean, median, standard deviation, minimum and maximum were provided for the efficacy parameters: HIV-1 RNA viral load, CD4 cell count and CD4%. Percentages of patient with HIV-1 RNA VL <400 copies/mL and that with HIV-1 VL<50 copies/mL were obtained using the Snapshot approach[1]. All the secondary efficacy endpoints will be reported for three age groups: (3-<6, 6-<12, 12-<18). A post-hoc efficacy analyses by regions (Botswana and Germany/USA) have been performed because of a median of ten months gap between the PK phase and the OEP for the Botswanan patients.

3.2.3 Results and Conclusions

3.2.4.1 Patient Disposition, Demographic and Baseline Characteristics for PK Phase

The 1100.1518 enrolled 90 pediatric HIV-1 patients. Among them 85 took at least one study drugs and was considered as Full Analysis Set (FAS). Among them 80 (94%) completed the PK evaluations at Day 22, and five patients were discontinued during the PK phase. There were forty patients entered the OEP for Week 24 efficacy evaluations. One patient (2.5%) discontinued due to AE and thirty-nine patients completed the OEP. Table 1 provides a summary of patient disposition by three age groups and by the two phases (PK and OEP).

Demographics, baseline characteristics, AIDS defining illness and history of ART for the PK phase are summarized below.

Table 2 summarizes demographics by age groups for the PK phase. The FAS in the 1100.1518 consists 60 pediatric patients in Botswana, 12 in South Africa, 12 in Germany and 2 in the USA. Overall, the study population included 92.9% Blacks, 55% females, 98.8% non-Hispanics.

Table 3 summarizes baseline characteristics by age groups for the PK phase. At entry, the median CD4+ cell counts were 1333, 942 and 650 cells/mm^3 respectively for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years. Overall, 87% of the patients had CD4+ 500 cells/mm^3 or more. The median BSAs were 0.7, 0.9 and 1.4 respectively for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years.

Table 4 summarizes AIDS defining illness and history of ART. Overall, 48% of the patients had AIDS defining illness at entry. The percentages of patients with AIDS defining illness were 27%, 39% and 73%, respectively, for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years. This FAS population had a median of five years and a range of 0-12 years of the treatment with NVP. 95.3% of patients had 3TC-containing regimen, followed by 70.6% with AZT-containing regimen. The AZT+3TC (76.6%) and d4T+3TC (16.5%) were two main NNRTI background regimens.

Table 1. Disposition of Patients

	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				
Enrolled				90
Treated	26	26	33	85
Completed at Day 22[1]	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	1 (3.8)	1 (3.8)	1 (3.0)	3 (3.5)
Disposition in the OEP				
Entered into OEP	12	16	12	40
Completed OEP Week 24[2]	11 (91.7)	16 (100.0)	12 (100.0)	39 (97.5)
AE	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.5)

1. Day 22: between Day 18 to Day 30 from Day 1.
2. OEP Week 24 defined as Day 127 to Day 210 from OEP Day 1 (Visit 9 for Botswana and Visit 8 for Germany/USA), see "\\CDSESUB1\EVSPROD\NDA201152\0035\m5\datasets\1100-1518-24wk\analysis\programs\BUILDINDER24.SAS ".

Table 2. PK Phase: Baseline Demographics[1]

	3 to <6 yr N=26	6 to <12 yr N=26	12 to <18 yr N=33	Total N=85
Sex				
Male	13 (50.0)	12 (46.2)	13 (39.4)	38 (44.7)
Female	13 (50.0)	14 (53.8)	20 (60.6)	47 (55.3)
Race				
Black	25 (96.2)	22 (84.6)	32 (97.0)	79 (92.9)
White	1 (3.8)	4 (15.4)	1 (3.0)	6 (7.1)
Hispanic				
Yes	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
No	25 (96.2)	26 (100.0)	33 (100.0)	84 (98.8)
Country				
Botswana	20 (76.9)	16 (61.5)	24 (72.7)	60 (70.5)
South Africa	2 (7.7)	4 (15.4)	6 (18.2)	12 (14.1)
Germany	4 (15.4)	6 (23.1)	2 (6.1)	12 (14.1)
USA	0 (0.0)	0 (0.0)	2 (6.1)	2 (2.4)

1. Source: Reviewer's analysis.

Table 3. PK Phase: Baseline Characteristics[1,2]

	3 to <6 yr N=26	6 to <12 yr N=26	12 to <18 yr N=33	Total N=85
BSA (m^2)				
Minimum	0.6	0.7	1.0	0.6
maximum	0.8	1.4	1.7	1.7
median	0.7	0.9	1.4	1.0
mean	0.7	0.9	1.4	1.0
std	0.1	0.2	0.2	0.3
Height (cm)				
Minimum	87.0	110.0	139.0	87.0
maximum	117.0	149.0	176.0	176.0
median	104.0	127.0	158.0	129.0
mean	103.8	125.8	157.8	131.5
std	7.1	9.6	8.4	24.2
Weight (kg)				
Minimum	13.0	17.7	24.0	13.0
maximum	22.1	47.0	62.2	62.2
median	15.8	25.3	45.5	27.5
mean	16.0	25.8	45.2	30.3
std	2.1	6.6	9.6	14.4
CD4 Cell Count (cells/mm^3)				
Minimum	597.1	495.2	207.3	207.3
maximum	2056.8	1859.4	1567.0	2056.8
median	1333.3	942.5	650.3	931.5
mean	1322.0	977.7	715.0	977.0
std	391.9	311.5	335.9	424.6
CD4 Cell Count (cells/mm^3) – N(%)				
Missing	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
>200 to 350	0 (0.0)	0 (0.0)	4 (12.1)	4 (4.7)
>350 to 500	0 (0.0)	1 (3.8)	5 (15.2)	6 (7.1)
>500	25 (96.2)	25 (96.2)	24 (72.7)	74 (87.1)
CD4%				
Minimum	18.5	21.2	13.4	13.4
maximum	52.1	48.9	45.6	52.1
median	42.1	36.8	35.0	36.1
mean	39.2	36.7	33.1	36.0
std	8.7	7.7	6.9	8.0
CD4% - N(%)				
Missing	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
≤15%	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.2)
>15% to 25%	1 (3.8)	2 (7.7)	3 (9.1)	6 (7.1)
>25%	24 (92.3)	24 (92.3)	29 (87.9)	77 (90.6)

1. Source: Reviewer's analysis.
2. One subject in Age group 3 to <6 yr had missing in baseline CD4 cell count and CD4%.

Table 4. PK Phase: History of ART/AIDS and Baseline Background Therapy Regimen[1]

	3 to <6 yr N=26	6 to <12 yr N=26	12 to <18 yr[2] N=33	Total N=85
Background Therapy Regimen N (%)				
AZT	14 (53.8)	19 (73.1)	27 (81.8)	60 (70.6)
3TC	26 (100.0)	25 (96.2)	30 (90.9)	81 (95.3)
D4T	9 (34.6)	3 (11.5)	3 (9.1)	15 (17.6)
DDI	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.2)
ABC	3 (11.5)	2 (7.7)	2 (6.1)	7 (8.2)
TDF	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.2)
FTC	1 (3.8)	0 (0.0)	1 (3.0)	2 (2.4)
Background Therapy Regimen N (%)				
AZT+3TC	14 (53.8)	19 (73.1)	27 (81.8)	60 (70.6)
D4T+3TC	9 (34.6)	3 (11.5)	2 (6.1)	14 (16.5)
Other	3 (11.5)	4 (15.4)	4 (12.1)	11 (12.9)
NVP as the first HARRT Regimen N (%)				
Yes	23 (88.5)	21 (80.8)	26 (78.8)	70 (82.4)
No	3 (11.5)	5 (19.2)	7 (21.2)	15 (17.6)
History of AIDS-defining illness N (%)				
Yes	7 (26.9)	10 (38.5)	24 (72.7)	41 (48.2)
No	19 (73.1)	16 (61.5)	9 (27.3)	44 (51.8)
Years on NVP				
Minimum	0.3	0.0[2]	0.3	0.0
maximum	5.6	8.4	12.0	12.0
median	3.4	5.4	6.2	5.0
mean	3.2	4.5	5.6	4.5
std	1.5	2.4	2.4	2.3
Years on NVP N (%)				
<2yr	6 (23.1)	5 (19.2)	3 (9.1)	14 (16.5)
2 to <4 yr	13 (50.0)	3 (11.5)	4 (12.1)	20 (23.5)
4 to <6 yr	7 (26.9)	11 (42.3)	9 (27.3)	27 (31.8)
≥6 yr	0 (0.0)	7 (26.9)	17 (51.5)	24 (28.2)

1. Source: Reviewer's analysis.
2. One patient in Botswana (010197) had no history of NVP IR treatment at baseline.

3.2.4.2 Time Gap Between PK Phase and OEP

After the PK phase, Botswanan patients did not received NVP XR on time because of a prolonged approval time of an OEP IC form by the Botswana health authority. In other words, there was a delay of entering the OEP for the Botswanan patients, compared to the patients from Germany/USA.

Table 5 summarizes the statistics between OEP Day 1 and Day 1 in PK phase for the forty patients. Twenty-eight Botswana patients had a median delay of 323 days (46.1 weeks or 10.6 months) between Day 1 of OEP and Day 1 in the PK phase while the twelve patients from Germany/USA had a median of 15 days. This reviewer's results were similar to those by the sponsor.

Table 5. Duration between PK Phase to OEP Day 1

	N	median	Minimum	maximum	mean	Std
Duration between OEP Day 1 and PK Day 1[1]						
Botswana	28	323	264	384	318	37
Germany/USA	12	35	31	40	35	3
Duration between OEP Day 1 and PK Day 22[1]						
Botswana	28	303	244	361	298	37
Germany/USA	12	15	10	18	15	2
Sponsor's (Source: Table 3.1.1.2:1, Page 23 of 49 U11-3384-01)						
Botswana	28	302	250	360		

1. **Reviewer's analysis, unit days.**

3.2.4.3 OEP: Demographic and Baseline Characteristics

The demographics, baseline characteristics, AIDS defining illness and history of ART for the OEP are respectively in Tables 6-8, similar to those for the PK phase.

The FAS in the OEP of 1100.1518 consists 40 pediatric patients, 28 in Botswana, 10 in Germany and 2 in the USA. Overall, the study population included 87.5% Blacks, 55% females, 100% non-Hispanics. The demographics for the two geographic regions Botswana and Germany/USA were also provided in the second part of Table 6.

Table 7 summarizes baseline characteristics by age groups for the OEP. At entry, the median CD4 cell counts were 1132, 907 and 620 cells/mm^3 respectively for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years. Overall, 87.5% of the patients had 500 cells/mm^3 or more in CD4 cell count. The median BSAs were 0.7, 0.9 and 1.3 respectively for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years. These statistics appeared to be similar to those in the FAS for the PK phase.

Table 8 summarizes AIDS defining illness and history of ART. Overall, 45% of the patients had AIDS defining illness at entry. The percentages of patients with AIDS defining illness were 25%, 37.5% and 75%, respectively, for patients in the age groups 3 to 6 years, 6 to < 12 years, and 12 to < 18 years. This population had a median of 5.2 years and a range of 0-12 years of the treatment with NVP. The AZT+3TC (60%) and D4T+3TC (17.5%) were the two main NNRTI background regimens. Among the individual ART background drugs, 95% of patients had 3TC-containing regimen, followed by 60% with AZT-containing regimen. In addition, 18 (45%) patients were assigned to NVP XR 200 mg QD regimen, 12 to 300 mg QD regimen, and 10 to 400 mg QD regimen.

Table 6. OEP: Baseline Demographics[1]

	3 to <6 yr	6 to <12 yr	12 to <18 yr	Total
1. Overall				
N	12	16	12	40
Sex				
Male	6 (50.0)	8 (50.0)	4 (33.3)	18 (45.0)
Female	6 (50.0)	8 (50.0)	8 (66.7)	22 (55.0)
Race				
Black	12 (100.0)	12 (75.0)	11 (91.7)	35 (87.5)
White	0 (0.0)	4 (25.0)	1 (8.3)	5 (12.5)
Hispanic				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	12 (100.0)	16 (100.0)	12 (100.0)	40 (100.0)
Country				
Botswana	9 (75.0)	10 (62.5)	9 (75.0)	28 (70.0)
Germany	3 (25.0)	6 (37.5)	1 (8.3)	10 (25.0)
USA	0 (0.0)	0 (0.0)	2 (16.7)	2 (5.0)
2. Botswana				
N	9	10	9	28
Sex				
Male	6 (66.7)	5 (50.0)	3 (33.3)	14 (50.0)
Female	3 (33.3)	5 (50.0)	6 (66.7)	14 (50.0)
Race				
Black	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
White	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	9 (100.0)	10 (100.0)	9 (100.0)	28 (100.0)
3. Germany/USA				
N	3	6	3	12
Sex				
Male	0 (0.0)	3 (50.0)	1 (33.3)	4 (33.3)
Female	3 (100.0)	3 (50.0)	2 (66.7)	8 (66.7)
Race				
Black	3 (100.0)	2 (33.3)	2 (66.7)	7 (58.3)
White	0 (0.0)	4 (66.7)	1 (33.3)	5 (41.7)
Hispanic				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	3 (100.0)	6 (100.0)	3 (100.0)	12 (100.0)
Country				
US	0 (0.0)	0 (0.0)	2 (66.7)	2 (16.7)
Germany	3 (100.0)	6 (100.0)	1 (33.3)	10 (83.3)

1. Source: Reviewer's analysis, n(%).

Table 7. OEP: Baseline Characteristics[1]

	3 to <6 yr N=12	6 to <12 yr N=16	12 to <18 yr N=12	Total N=40
BSA (m^2)				
Minimum	0.6	0.7	1.0	0.6
maximum	0.8	1.4	1.7	1.7
median	0.7	0.9	1.3	0.9
mean	0.7	0.9	1.3	1.0
std	0.1	0.2	0.2	0.3
Height (cm)				
Minimum	94.0	110.0	140.0	94.0
maximum	116.0	149.0	167.0	167.0
median	104.5	124.0	156.0	124.0
mean	105.8	125.3	155.3	128.5
std	6.9	10.8	7.7	21.4
Weight (kg)				
Minimum	13.7	17.7	24.0	13.7
maximum	22.1	47.0	60.4	60.4
median	16.8	24.4	40.5	23.4
mean	16.8	25.4	40.1	27.2
std	2.3	7.6	9.3	11.6
CD4 Cell Count (cells/mm^3)				
Minimum	604.5	446.0	354.5	354.5
maximum	1561.0	1496.0	1874.0	1874.0
median	1132.3	907.0	619.8	886.5
mean	1173.4	905.2	717.4	929.3
std	340.7	235.6	435.6	374.2
CD4 Cell Count (cells/mm^3) – N(%)				
>350 to 500	0 (0.0)	1 (6.3)	4 (33.3)	5 (12.5)
>500	12 (100.0)	15 (93.8)	8 (66.7)	35 (87.5)
CD4%				
Minimum	31.0	27.8	24.0	24.0
maximum	52.2	47.6	44.3	52.2
median	40.4	38.9	36.4	37.9
mean	40.4	38.2	34.5	37.8
std	5.4	6.3	6.3	6.3
CD4% - N(%)				
>15% to 25%	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.5)
>25%	12 (100.0)	16 (100.0)	11 (91.7)	39 (97.5)

1. Source: Reviewer's analysis.

Table 8. OEP: History of ART/AIDS and Baseline Background Therapy Regimen[1]

	3 to <6 yr N=12	6 to <12 yr N=16	12 to <18 yr[2] N=12	Total N=40
Background Therapy Regimen-N (%)[2]				
AZT	5 (41.7)	10 (62.5)	9 (75.0)	24 (60.0)
3TC	12 (100.0)	15 (93.8)	11 (92.7)	38 (95.0)
D4T	5 (41.7)	1 (6.3)	3 (25.0)	9 (22.5)
DDI	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.5)
ABC	2 (16.7)	2 (12.5)	2 (16.7)	6 (15.0)
TDF	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.5)
FTC	1 (8.3)	1 (6.3)	0 (0.0)	2 (5.0)
Background Therapy Regimen-N (%)				
AZT+3TC	5 (41.7)	10 (62.5)	9 (75.0)	24 (60.0)
D4T+3TC	5 (41.7)	1 (6.3)	1 (8.3)	7 (17.5)
Other	2 (16.7)	5 (31.3)	2 (16.7)	9 (22.5)
NVP as the first HARRT Regimen-N (%)				
Yes	10 (83.3)	13 (81.3)	9 (75.0)	32 (80.0)
No	2 (16.7)	3 (18.8)	3 (25.0)	8 (20.0)
History of AIDS-defining illness-N (%)				
Yes	3 (25.0)	6 (37.5)	9 (75.0)	18 (45.0)
No	9 (75.0)	10 (62.5)	3 (25.0)	22 (55.0)
Years on NVP				
minimum	0.8	0.0	3.9	0.0
maximum	5.6	8.4	12.0	12.0
median	3.5	5.3	6.7	5.2
mean	3.3	4.4	6.8	4.8
std	1.3	2.5	2.0	2.4
Years on NVP-N (%)				
<2yr	2 (16.7)	3 (18.8)	0 (0.0)	5 (12.5)
2 to <4 yr	7 (58.3)	2 (12.5)	1 (8.3)	10 (25.0)
4 to <6 yr	3 (25.0)	7 (43.8)	3 (25.0)	13 (32.5)
≥6 yr	0 (0.0)	4 (25.0)	8 (66.7)	12 (30.0)
NVP XR QD Regimen-N (%)				
200 QD XR	9 (75.0)	7 (43.8)	2 (16.7)	18 (45.0)
300 QD XR	3 (25.0)	5 (31.3)	4 (33.3)	12 (30.0)
400 QD XR	0 (0.0)	4 (25.0)	6 (50.0)	10 (25.0)

1. Source: Reviewer's analysis.

3.2.4.4 OEP: Compliance and Duration of Treatment with NVP XR

This reviewer obtained the basic statistics for compliance with NVP XR during the OEP. A total of 157 data points were obtained, 74 for the 28 Botswanan patients, and 83 for 12 patients from Germany/USA. The median (minimum, maximum) compliance with NVP XR are 100% (56%, 106%) for the Botswanan patients, and 100% (91%, 109%) for the patients from Germany/USA. The results by visit for Visit Number 100 (OEP_1) to 150 (OEP_8) are summarized in Table 9 below. During the OEP, all patients except one from Germany/USA had compliance 80% or more.

The sponsor reported "*…compliance with dosing was 80 to 120% for 97.5% (39/40) of patients during the OEP*", and "*All children in the 3 to <6 year age group received either 2 or 3 NVP XR 100 mg tablets and had 100% cumulative treatment adherence during the OEP*." (In Section (Section 2.7.3 Summary of Clinical Efficacy, Page 9 of 49).

Table 9. NVP XR Compliance Since the End of PK Phase*

Region	# <100%	%	#≥100%	%	Missing	%
Botswana						
end of PK	0	0.0	28	100.0	0	0.0
OEP_1	6	21.4	22	78.6	0	0.0
OEP_2	4	14.3	23	82.1	1	3.6
OEP_3	9	32.1	18	64.3	1	3.6
Germany/USA						
end of PK	1	8.3	11	91.7	0	0.0
OEP_1	0	0.0	12	100.0	0	0.0
OEP_2	4	33.3	7	58.3	1	8.3
OEP_3	5	41.7	6	50.0	1	8.3
OEP_4	4	33.3	8	66.7	0	0.0
OEP_5	5	41.7	7	58.3	0	0.0
OEP_6	6	50.0	6	50.0	0	0.0
OEP_7	3	25.0	6	50.0	3	25.0
OEP_8	5	41.7	1	8.3	6	50.0

***. Source: reviewer's analyses.** OEP_j (j=1 to 8, visit number 100 to 150 during OEP).

Table 10 summarizes the basic statistics for the duration of treatment with NVP XR in the OEP by this reviewer. Median duration of 33.2 weeks in Botswanan patients and 80.4 weeks in patients from Germany/USA were obtained.

The sponsor reported the duration of treatment with NVP XR in the OEP as shown below:

- Median duration of 33 weeks (Section 6.2, NVP label document)
- 32.7 weeks in Botswanan patients and 82.1 weeks in Gemany/US pts (Page 6, U11-3309-01)

Please note that the median treatment duration of 80.4 weeks in patients from Germany/USA by this reviewer was slightly shorter than a median of 82.1 weeks reported by the sponsor.

- The only SAS variable for the treatment duration with NVP XR is 'exdur'. One can found it in the ADaM dataset 'adameff.xpt'. This variable can not be used directly since it may include the 10 months waiting time for the 28 Botswanan patients. If one uses this variable, a much longer median time will be obtained.

Table 10. OEP: Duration of Treatment with NVP XR[1]

	N	median	minimum	Maximum	mean	std
Overall	40	33.9	9.7	88.6	45.8	22.1
NVP XR Dose						
200 mg QD	18	33.8	9.7	88.6	37.8	18.6
300 mg QD	12	33.8	29.7	88.4	44.5	22.6
400 mg QD	10	70.0	32.4	81.7	61.7	20.8
Country						
Botswana	28	33.2	9.7	33.9	32.0	4.6
Germany/USA	12	80.4	64.7	88.6	78.0	8.4
Age						
3-<6 yr	12	33.8	9.7	88.4	43.0	24.1
6-<12 yr	16	33.9	29.7	88.6	49.8	23.5
12-<18 yr	12	33.8	29.7	81.7	43.3	19.1

1. Reviewer's analyses. Treatment weeks with NVP XR since the Day 1 of OEP.

3.2.4.5 Efficacy Endpoints and Results

The efficacy results in the PK phase by this reviewer and by the sponsor are summarized in Table 11. There are some numerical discrepancies. For example, the proportions of patients with HIV-1 RNA VL < 50 copies/mL at Day 22 was 97.6% by this reviewer, and 98.7% by the sponsor.

Table 12 summarizes efficacy results through the 24 weeks of treatment with NVP XR-containing regimens. One patient discontinued prior to Week 24 due to AE, and 39 patients (97.5%) continued maintaining their virologic suppression (HIV-1 VL < 50 copies/mL) with the (2.5^{th}, 97.5^{th}) percentile interval of (0.1%,13.2%). For the subgroup results, please refer to Table 12. Apparently, no analyses for percentage of patients with HIV-1 VL <400 copies/mL at Week 24 were necessary.

Table 13 summarizes CD4 cell count and CD4% at OEP Day 1, OEP Week 24 and the changes. The imputations of missing are based on the principle of Last-Observation-Carried-Forward (LOCF) approach. It appears that the immunologic functions were also well maintained. Overall, the median change from baseline in CD4+ was 32 cells/mm^3 with 95% CI of (-781,458) cells/mm^3, and the median change from baseline in CD4% was -1% with 95% CI of (-9, 5)%.

No significant or meaningful differences in these efficacy endpoints were found regarding age or geographic region subgroups.

Table 11. PK Phase: HIV RNA VL, CD4+ and CD4%[1,2]

	Reviewer's	Sponsor's
1. Proportion of Patients with VL <50 copies/mL		
Day 1 (NVP IR/XR)	81/83 (97.6)	83/85 (97.6)
Day 11 (NVP IR/XR)	77/83 (92.8)	77/83 (92.8)
Day 22	81/83 (97.6)	78/79 (98.7)
200 QD XR	35/36 (97.2)	35/35 (100.0)
300 QD XR	20/21 (95.2)	19/20 (95.0)
400 QD XR	26/26 (100.0)	24/24 (100.0)
2. Median CD4+ cell count/mm^3		
Day 1 (NVP IR/XR)	896.0	925.1 (929.3)
Day 11 (NVP IR/XR)	868.0	
200 QD XR	1101.5	
300 QD XR	830.5	
400 QD XR	806.0	
Day 22	872.0	
200 QD XR	1004.0	
300 QD XR	809.0	
400 QD XR	822.0	
3. Median CD4%		
Day 1 (NVP IR/XR)	37.2	
Day 11 (NVP IR/XR)	37.6	
200 QD XR	39.0	
300 QD XR	39.6	
400 QD XR	36.1	
Day 22	37.5	
200 QD XR	35.1	
300 QD XR	37.7	
400 QD XR	36.8	

1. Source: Reviewer's analyses.
2. Day 1 CD4+ or CD4% are mean values for those with more than one values.

Table 12. OEP: Efficacy Endpoints At Week 24[a,b]

1. Proportion of Patients with VL <50 copies/mL[c]	
Overall	39/40 (97.5)
200 QD XR	17/18 (94.4)
300 QD XR	12/12 (100.0)
400 QD XR	10/10 (100.0)
[redacted] (b) (4)	
Germany/USA	12/12 (100.0)
Botswana	27/28 (96.4)
2. Median Change from Baseline in CD4+ cell count/mm^3 [d]	
Overall (40)	-2.5
200 QD XR (18)	-17.0
300 QD XR (12)	-32.5
400 QD XR (10)	54.5
[redacted] (b) (4)	
Germany/USA (12)	-6.0
Botswana (28)	-2.5
3. Median Change from Baseline in CD4% [d]	
Overall (40)	-1.4
200 QD XR (18)	-2.3
300 QD XR (12)	-1.0
400 QD XR (10)	-0.8
[redacted] (b) (4)	
Germany/USA (12)	-1.9
Botswana (28)	-1.0

a. Source: Reviewer's analyses.
b. Week 24: Day 140 to Day 196 from PK phase Day 1 for Germany/USA patients; Day 140 to Day 196 from OEP Day 1 for Botswana patients.
c. "Missing as Failure" approach.
d. Baseline-observation-carried-forward for missing.

Table 13. OEP: Baseline CD4+ (CD4%) and CD4+ (CD4%) at Week 24[1]

	n	mean	std	median	minimum	maximum
CD4+ (cells/mm^3) at OEP Day 1						
Overall	40	905	374	835	379	1614
[redacted]						(b) (4)
CD4+ (cells/mm) at OEP Week 24						
Overall	40	885	353	805	359	1988
[redacted]						(b) (4)
Change from OEP baseline in CD4+ (cells/mm) to OEP Week 24						
Overall	40	-20	293	32	-812	462
[redacted]						(b) (4)
CD4% at OEP Day 1						
Overall						
[redacted]						(b) (4)
CD4% at OEP Week 24[2]						
Overall	40	36	7	37	25	50
[redacted]						(b) (4)
Change from OEP baseline in CD4% to OEP Week 24						
Overall	40	-1	4	-1	-10	6
[redacted]						(b) (4)

1. Source: Reviewer's analysis, 'LOCF' to impute missing for Patient '10230'.
2. Recoding Week 24 time window: Day 141 to Day 196 from OEP Day 1 where variable 'anaday' for Germany/USA and 'oepday' for Botswana patients were used.

3.3 Evaluation of Safety

Please refer to clinical reviewer's analyses for safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The OEP in Study 1100.1518 consists of forty patients. Hence, it is not practical to conduct other subgroup analyses except for the age groups and geographic region 'Botswana' or 'Germany/USA'. The efficacy results by age and region were included in Section 3.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A total of 40 patients were enrolled to the OEP to receive extended release VIRAMUNE (NVP XR) for efficacy evaluation. Of these 40 patients, 12 patients were in the 3 to < 6 years group, 16 in the 6 to < 12 years group, and 12 in the 12 to < 18 years group. The patients received a median of 34 weeks treatment with NVP XR-containing regimens. One patient discontinued prior to Week 24 due to AE, and 39 patients (97.5%) continued maintaining HIV-1 VL < 50 copies/mL with the (2.5^{th} , 97.5^{th}) percentile interval of (0.1%,13.2%). This demonstrated the virologic suppression was well maintained. In addition, the immunologic functions were also well maintained. Overall, the median change from baseline in CD4+ was 32 cells/mm^3 with 95% CI of (-781,458) cells/mm^3, and the median change from baseline in CD4% was -1% with 95% CI of (-9, 5)%. No significant or meaningful differences in these efficacy endpoints were found regarding age or geographic region subgroups.

Due to the nature of this open-label, switching study, the statistical evaluation of antiviral activity and immunologic responses has been descriptive. No statistical issue was identified.

5.2 Conclusions and Recommendations

(b) (4)

6. APPENDICES

6.1 SAS List File for 'TRTA'

Checking TRTA in adameff.xpt 08:58
Thursday, February 23, 2012 89

The FREQ Procedure

Treatment actual received

TRTA	Frequency	Percent	Cumulative Frequency	Cumulative Percent
12-<18 yr	33	38.82	33	38.82
3-<6 yr	26	30.59	59	69.41
6-<12 yr	26	30.59	85	100.00

Frequency Missing = 5

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