

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201152Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA Serial Number:** 201,152

**Drug Name:** Viramune<sup>®</sup> XR<sup>™</sup> (nevirapine) extended-release tablets

**Indication(s):** Treatment of [REDACTED]<sup>(b) (4)</sup> HIV-1 infected subjects

**Applicant:** Boehringer Ingelheim, Inc.

**Date(s):** Submitted: June 3, 2010  
PDUFA Goal Date: April 3, 2011

**Review Priority:** Standard

**Biometrics Division:** Division IV

**Statistical Reviewer:** Susan Zhou, Ph.D. (HFD-725)

**Concurring Reviewers:** Greg Soon, Ph.D. (HFD-725)

**Medical Division:** DAVP

**Clinical Team:** Peter Miele, M.D. (HFD-530)

**Project Manager:** Amalia Himaya (HFD-530)

**Keywords:** Non-inferiority, Taqman and Amplicor-corrected HIV-1 assays, TLOVR and Snapshot, ARV-naïve HIV-1 infected patients, Sustained Virologic Response, Agreement

## Table of Contents

<b>U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES .....</b>	<b>1</b>
<b>FOOD AND DRUG ADMINISTRATION .....</b>	<b>1</b>
<b>STATISTICAL REVIEW AND EVALUATION .....</b>	<b>1</b>
<b>LIST OF TABLES.....</b>	<b>3</b>
<b>LIST OF FIGURES.....</b>	<b>3</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>4</b>
<b>2 INTRODUCTION .....</b>	<b>6</b>
2.1 OVERVIEW.....	6
2.2 DATA SOURCES .....	6
<b>3 STATISTICAL EVALUATION .....</b>	<b>7</b>
3.1 DATA AND ANALYSIS QUALITY .....	7
3.1.1 <i>Amplicor-corrected Procedure for Re-testing</i> .....	7
3.1.2 <i>Some Data Problems</i> .....	8
3.2 EVALUATION OF EFFICACY .....	8
3.2.1 <i>Study Design and Endpoints</i> .....	8
3.2.2 <i>Statistical Methodologies</i> .....	10
3.2.3 <i>Patient Disposition, Demographic and Baseline Characteristics</i> .....	11
3.2.4 <i>Efficacy Results</i> .....	14
3.3 EVALUATION OF SAFETY .....	19
<b>4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>19</b>
4.1 GENDER, RACE, AGE, ETHNIC AND GEOGRAPHIC REGION .....	19
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS .....	20
4.3 COMPARISONS OF DIFFERENT ESTIMATION METHODOLOGIES AND HIV-1 RNA ASSAY PROFILES VIA AGREEMENT STATISTICS .....	21
<b>5 SUMMARY AND CONCLUSIONS .....</b>	<b>23</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	23
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	24
<b>6 APPENDICES.....</b>	<b>24</b>
6.1 REFERENCES.....	24
<b>7 SIGNATURES/DISTRIBUTION LIST (OPTIONAL).....</b>	<b>25</b>

## LIST OF TABLES

	<b>Page</b>
Table 1. 1100.1486: Randomization and Disposition Through Week 48* .....	12
Table 2. 1100.1486: Subject Demographics and Baseline Characteristics* .....	13
Table 3. Outcomes at Week 48 in Study 1100.1486.....	14
Table 4. 1100.1486: SVR through Week 48 with LLOQ 50 copies/mL* .....	15
Table 5. 1100.1486: SVR through Week 48 with LLOQ 400 copies/mL* .....	16
Table 6. 1100.1486: Estimated Hazard Ratio of Losing Virologic Response Using Cox Model* 16	16
Table 7. Observed and Estimated Mean Change from Baseline to Week 48 in CD4+* .....	17
Table 8. Subgroup Analyses of Observed SVR at Week 48* .....	19
Table 9. Subgroup Analyses of Treatment Difference in Week 48 SVR* .....	20
Table 10. 1100.1486: Subgroup Analyses of Virological Responders at Week 48 (Snapshot)* .	21
Table 11. 1100.1486: Concordance and Discordance in SVR at Week 48* .....	22

## LIST OF FIGURES

	<b>Page</b>
Figure 1: 1100.1486: K-M (TLOVR, LLOQ 50 copies/mL, Amplicor-corrected Assay) .....	18
Figure 2: 1100.1486: K-M (LLOQ 50 copies/mL, TaqMan Assay) .....	18

## 1 EXECUTIVE SUMMARY

*This is an integrated executive summary based on statistical review of Study 1100.1486 and Study 1100.1526.*

Boehringer Ingelheim Pharmaceutical Inc. (BIPI) submitted NDA 201,152 to apply for the approval of 400 mg QD nevirapine extended release formulation (VIRAMUNE XR, NVP XR) in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. Consideration of approval for this NDA is based on the antiviral efficacy and safety from one principal clinical trial 1100.1486 and one supportive trial 1100.1526, both were randomized, controlled, non-inferiority Phase III trials in adult patients with HIV-1 infection. The 200 mg BID nevirapine 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 pivotal trial 1100.1486 was conducted double-blinded in treatment-naïve patients. 1011 patients were randomized and treated with 400 mg QD NVP XR formulation or the 200 mg BID NVP IR, both in combination with Truvada<sup>®</sup> (emtricitabine and tenofovir disoproxil fumarate) QD after a 2-week lead-in phase treatment with NVP IR 200 mg QD. After 48 week treatment, 405/505 (80.2%) of NVP XR patients and 380/506 (75.1%) of NVP IR patients achieved HIV-1 RNA < 50 copies/mL (sustained virologic response), with a difference of 4.9% with 95% CI: (-0.2%, 10.1%) adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL). In addition, mean change from baseline in CD4<sup>+</sup> cell count adjusting for baseline HIV-1 viral load stratum was 206 cells/mm<sup>3</sup> and 191 cells/mm<sup>3</sup> for the groups receiving NVP XR and NVP IR respectively. The virologic responses at Week 48 were obtained using snapshot algorithm on HIV-1 RNA via Amplicor-corrected virologic assay (snapshot algorithm/Amplicor-corrected HIV assay).

- The lower bounds of the difference was greater than the pre-specified non-inferiority margins: -10%, demonstrating the non-inferiority of NVP XR to NVP IR treatment among ARV-treatment naïve HIV-1 infected patients in 1100.1486.
- The non-inferiority of NVP XR to NVP IR in 1100.1486 was robust and numerically consistent regardless of HIV-1 RNA viral load assay and algorithm (TaqMan only or ‘Amplicor-corrected’), algorithms for the estimation of sustained virologic responses (the TLOVR algorithm or Snapshot approach), and the level of lower limit of quantification (LLOQ 50 or 400 copies/mL).
- Subgroup analysis on Week 48 sustained virologic response with respect to age, gender, race, ethnicity, and geographic region adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL) showed numerical benefit in the NVP XR group versus NVP IR group with a range of 2.3% to 9.3%. At 0.20 significance level, treatment by age, gender, race, geographic region interactions were not statistically significant different from zero. Likewise, treatment by baseline HIV-1 RNA strata or baseline CD4<sup>+</sup> ( $\leq$  or  $>$ 200 cells/mm<sup>3</sup>) were not statistically significant from zero.

The supportive trial 1100.1526 was conducted in an open-label manner in treatment-experienced patients. A total of 443 patients already on an antiviral regimen containing 200 mg BID NVP IR with HIV-1 RNA < 50 copies/mL were randomized in a 2:1 ratio to either switch to the 400 mg QD NVP XR formulation or continue on the 200 mg BID NVP IR, while remaining on their previous background therapy. According to the snapshot algorithm and Amplicor-corrected HIV assay, 281/295 (95.3%) of NVP XR patients and 139/148 (93.9%) of NVP IR patients had maintained virologic suppression (HIV-1 RNA < 50 copies/mL) by Week 24, with a difference of 1.3% in favor of NVP XR (95% CI: -3.5%, 6.1%) adjusting for the baseline background therapy.

- The lower bound of the treatment difference was greater than the pre-specified non-inferiority margin -12%, demonstrating the non-inferiority of NVP XR to NVP IR treatment among ARV-treatment experienced HIV-1 infected patients in 1100.1526.
- The non-inferiority of NVP XR to NVP IR in 1100.1526 were consistent regardless of HIV-1 RNA viral load assay and algorithm (TaqMan only or ‘Amplicor-corrected’), algorithms for the estimation of sustained virologic responses (the TLOVR algorithm or Snapshot approach), and different analysis data sets.
- Subgroup analysis on sustained virologic response (HIV-1 RNA < 50 copies/mL) by Week 24 with respect to baseline demographics (age, gender, race, and geographic region) or clinical characteristics (CD4+ cell count, CDC class, HIV-1 baseline viral load, nevirapine as first highly active antiretroviral therapy regimen, duration of previous NVP IR treatment, and type of previous background therapy) showed numerically similarities between the NVP XR and NVP IR groups. There is no apparent relationship between the proportion of sustained virologic responders at Week 24 and any baseline demographics or clinical characteristic.
- Due to the open-label design feature of Study 1100.1526, interpretation of the key underlying efficacy results is limited by the facts that patients were already on a NVP IR BID regimen and were virologically suppressed for at least 18 weeks prior to enrollment, and only selected specimens were assayed using both virologic methods (TaqMan and Amplicor) as a result of protocol change.

BIPI’s key efficacy results in the two trials can be replicated by the statistical reviewers. BIPI concluded that treatment with NVP XR 400 mg QD was non-inferior to treatment with NVP IR 200 mg BID. Based on the statistical evaluation of efficacy data in Studies 1100.1486 and 1100.1526, the statistical reviewers concur with BIPI’s conclusions.

This reviewer conducted the statistical review of efficacy data in Study 1100.1486. The statistical review of efficacy in Study 1100.1526 was performed by Lan Zeng. Please refer to her review document for details.

## 2 INTRODUCTION

### 2.1 Overview

Viramune<sup>®</sup> (Nevirapine, NVP) is a non-nucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) developed by Boehringer Ingelheim Pharmaceutical, Inc. (BIPI) for use in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. The 200 mg nevirapine immediate release tablet (VIRAMUNE, NVP IR) received marketing authorization in the US in 1996 for use in combination with nucleoside analogues in adults with HIV infection. The treatment is 200 mg once daily (QD) for 14 days and followed by 200 mg twice daily (BID), in combination with other ARV. An oral suspension formulation was approved in 1998. BIPI has developed an extended release tablet formulation, nevirapine XR (NVP XR), to be administered as 400 mg QD regimen. The current NDA seeks to register nevirapine XR tablet (VIRAMUNE XR) in the same indication as the NVP IR tablet.

BIPI's clinical development program of NVP XR to support efficacy and safety of NVP XR included two phase III studies: 1100.1486 and 1100.1526. The pivotal trial 1100.1486 was a randomized, double-blinded non-inferiority study assessing efficacy and safety of NVP XR QD versus NVP IR BID both in combination of Truvada (tenofovir and emtricitabine) in treatment-naïve patients. The support trial 1100.1526 was a randomized, open-label non-inferiority study assessing efficacy and safety of NVP XR among those virologically suppressed ARV-experienced HIV-1 infected patients who were already on NVP IR regimen at entry and were switched from NVP IR BID to NVP XR QD both in combination of background regimen.

This reviewer conducted the statistical review of efficacy in 1100.1486. The statistical review of efficacy in 1100.1526 was performed by Lan Zeng. Please refer to her review document for details.

### 2.2 Data Sources

The NDA201,152 was submitted electronically to the CDER Electronic Document Room (EDR) directory of "[\Cdsub1\evsprod\NDA201152](#)", including SAS datasets and all modules containing clinical study reports. In addition, BIPI submitted 15 SAS programs to "[\Cdsub1\evsprod\NDA201152\0005](#)" to demonstrate how the analysis datasets were generated from the CDISC SDTM (Standard Data Tabulation Model) datasets.

This reviewer conducted efficacy analyses, included the following aspects:

1. Reviewing protocols, statistical analysis plans, efficacy results and conclusions;
2. Performing efficacy analysis based on the SAS analysis and SDTM datasets; and
3. Verifying selected SAS programs for the generation of the analysis datasets.

### 3 STATISTICAL EVALUATION

This section summarizes the detailed efficacy review of the pivotal trial 1100.1486, entitled “a randomized, double-blind, double-dummy, parallel-group, active-controlled, multinational study to evaluate the antiviral efficacy and safety of 400 mg QD neVirapine Extended Release formulation compared to 200 mg BID (nevirapine) immediate release in combination with Truvada® in ARV-naïve HIV-1-infected patients (VERxVE)”.

#### 3.1 Data and Analysis Quality

##### 3.1.1 Amplicor-corrected Procedure for Re-testing

Prior to the initiation of Studies 1100.1486 and 1100.1526, the supporting central laboratory <sup>(b) (4)</sup> changed the primary test for HIV-1 viral load (VL) quantification from the Roche Cobas Amplicor HIV-1 Monitor version 1.5 Ultrasensitive assay (Amplicor) to the Roche Cobas TaqMan assay (TaqMan). During the conduct of the studies, information emerged that the TaqMan assay has different performance characteristics from those of the Roche Cobas Amplicor Ultrasensitive assay, especially at the low viral load range, a range important for assessment of trial endpoints [R09-1202, R09-1203, R09-1204, Module 2.7.5]. The TaqMan assay appears to detect a higher frequency of results greater than the limit of detection (48 copies/mL). As a result, before the submission of this NDA, BIPI proposed a procedure for re-testing the VL, and the procedure was concurred with the DAVP review team. In addition, it was agreed to use Amplicor-corrected assay data to estimate the primary efficacy endpoint.

The criterion for the selection of samples to be re-tested using the Amplicor assay were as follows.

- All Week 48 and Week 50 or 60 (if applicable) samples.
- Samples with Taqman results <200 copies/mL at Week 24, 32, and 40, including Taqman results of “<48 copies/mL” and “No HIV RNA detected.”
- For patients who discontinued or changed treatment before Week 48, samples were not re-tested, since these patients were considered treatment failures, in any case.
- Samples from visits before Week 24 were re-tested with Amplicor, if Taqman results were <200 copies/mL, and if the pattern during pre-Week 24 and/or including Weeks 24, 32, and 40 indicated that the possibility of Amplicor re-testing might detect an early confirmed viral load response, followed by failure.
- The TaqMan assay may underestimate the HIV-1 viral load in a small proportion of patients with specific point mutations, pre-treatment (screening and baseline) samples were designated for retesting with Amplicor, if pre-treatment samples had unexpectedly low viral load (<5000 copies/mL) by the TaqMan assay.

### 3.1.2 Some Data Problems

Overall, this reviewer could replicate the sponsor's results using submitted SAS datasets with a few exceptions as follows.

#### 1. Two different formats for a key variable 'USUBJID'

The current CDISC SDTM submission requires several key variables including a unique subject identifier 'USUBJID' so that different datasets could be merged for analysis. In 1100.1486 it appears that the 'USUBJID' in two datasets 'adameff.xpt' and 'snapshot.xpt' was constructed using variable 'study', '-' and 'ptno', while the rest of the datasets used 'study', '-0' and 'ptno' to construct 'USUBJID'. Due to different structures and lengths, recoding and reformat the key variable 'USUBJID' was needed before merging datasets for analysis. Otherwise, one needs to find other indicator variables with same format and length.

#### 2. Time Windows for some laboratory parameters such as CD4+

A SAS program 'build\_inder.sas' computed variables such as change from baseline in CD4+ cell count. The program doesn't indicate any changes in 'visit' or 'visit num' but directly used the visit number to specify visit weeks in the 'lb.xpt' where the original laboratory parameters were collected. As a result, slight numerical differences were observed between the sponsor's and the reviewer's.

- The time window at Week 48 for the Snapshot approach has a range between Day 309 and Day 365 or Week 44 to Week 52, as indicated in the SAS program 'build\_snapshot' and Section 16.1.9.1 Statistical analysis plan.
- The range for visit num 12 is Day 287-Day 413, and the range for visit num 13 is Day 371- Day 459 for CD4+ cell count in the 'lb.xpt'.

#### 3. Discrepancies in 'Virologic Failure' at Week 48

Per review team's requests, this reviewer verified the Week 48 outcomes using analysis datasets 'adameff.xpt' and 'snapshot.xpt' for three patients with genotypic mutations at the time of discontinuation. Different results were observed in the two datasets and in the report but the percentages of virologic failure for the two treatment groups in NVP XR label remain unchanged.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

The 1100.1486 was a randomized, double-blind, double-dummy, parallel-group, active-controlled, multinational trial to evaluate the antiviral efficacy and safety of 400 mg QD nevirapine extended release formulation compared to 200 mg BID nevirapine immediate release in combination with Truvada<sup>®</sup>. It had a two-week lead-in period where all eligible patients received NVP IR 200 mg QD. After that, patients were randomized in a ratio of 1:1 to either

NVP XR 400 mg QD or NVP IR 200 mg BID. The randomization was stratified by baseline HIV-1 viral load ( $\leq$  or  $>100,000$  copies/mL). The duration of the treatment is 48 weeks including the two week lead-in period for the primary objective, with an extension up through 144 weeks.

The 1100.1486 was conducted in Europe (50%), North America (29%), Latin America (11%) and Africa (10%). The study population was predominantly male (85%), Caucasian (75%) with a mean or median age of 38 years (range 18-71).

### **Primary Efficacy Endpoint and Analysis**

The primary efficacy endpoint was a sustained virologic response (SVR) through Week 48 with LLOQ 50 copies/mL.

- Initially, DAVP's Time to Loss Of Virologic Response (TLOVR) algorithm was planned for the estimation of the primary and some of the secondary efficacy endpoints, regarding SVRs (See Section 16.1.9.1 SAP and Further Statistical Considerations).
- Since 2010, the DAVP has suggested using snapshot approach<sup>1</sup> for the estimation of SVR and virologic failure (VF). The corresponding outcomes based on the snapshot approach have been used in HIV-1 drug labels.

In the TLOVR algorithm, a virologic response is defined by two consecutive measurements of VL  $< 50$  copies/mL, at least two weeks apart. A sustained virologic response has no virologic rebound or change of ARV therapy through Week 48. A virologic rebound is defined by two consecutive measurements of VL  $\geq 50$  copies/mL, at least two weeks apart, after a virologic response.

- A change of ARV therapy is defined as either a permanent discontinuation of study medicine NVP (ER or IR), addition of new ARV drugs, or alterations in background therapy.
- For the primary analysis, a change in the background therapy due to toxicity or intolerance clearly attributable to Truvada<sup>®</sup> is not considered failure.
- Patients who die, lost to follow-up, or change ARV drugs due to toxicity or intolerance not attributable to Truvada<sup>®</sup> are considered treatment failure at the time of those events.

In the SNAPSHOT algorithm, Week 48 time window is defined from Week 44 to Week 52 and the SVR is based on the HIV-1 RNA VL value in the Week 48 time window. This approach applied 'A non-completer equals failure' (NCF). Patients who have introduced a new ARV drug to the regimen (except for changes in the background regimen pre-specified in the trial protocol) have discontinued study, have been lost to follow-up, or for whatever reason have missing HIV RNA data should be considered as failure, i.e., to have HIV RNA levels above 50 copies/mL or 400 copies/mL depending on the endpoint of interest.

In general, missing HIV RNA data between study visits with values below the assay limit does not constitute treatment failure based on the TLOVR algorithm. Specifically, missing VL data between visits in snapshot will be regarded as above LLOQ.

The primary analysis of the primary endpoint will be based on the Amplicor/TaqMan profile, and is referred to as ‘Amplicor-corrected’ assay profile. When using this profile, patients with 24, 32, 40 and 48 week Amplicor Test generated viral loads of <50 copies/mL will be classified as virologic responders at Week 48 regardless of pre-Week 24 TaqMan Test results.

The baseline HIV-1 viral load was defined as the maximum of screening viral load or Day 0 (the day a patient starts treatment) viral load.

### **Secondary Efficacy Endpoints**

Secondary efficacy endpoints include the following:

1. Time-to-loss-of-virologic-response (TLOVR) with LLOQ 50 copies/mL;
2. SVR through Week 48 with LLOQ 400 copies/mL;
3. Time-to-virologic-response (TVR) with LLOQ 50 copies/mL;
4. Time to new AIDS or AIDS-related progression event or death (TAIDS);
5. Change from baseline in VL and CD4+ cell count at each visit; and
6. Treatment emergent NNRTI and NRTI mutations.

Last Observation Carried Forward (LOCF) approach was used to impute missing values for HIV-1 RNA VL and CD4+ cell count at Visit 3 or beyond, resulting no baseline value carried forward. Change from baseline at Week 48 in VL and CD4+ will be compared between NVP XR and NVP IR groups using ANCOVA adjusting for baseline viral load.

### **3.2.2 Statistical Methodologies**

#### Study Population for Analysis

Three study populations were defined in the Study 1100.1486 protocol: Treated Set (TS), Full Analysis Set (FAS) and Per Protocol Set (PPS).

The TS included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment, including the lead-in nevirapine treatment.

The FAS was a subset of the TS that included all randomized patients who took at least one dose of randomized (blinded) investigational treatment. This data set excluded patients who took open-label lead-in nevirapine IR QD, but dropped out prior to randomization or prior to taking the first dose of randomized (blinded) nevirapine XR or nevirapine IR after randomization.

The PPS was a subset of the FAS, excluding patients with important protocol violations in the FAS.

In the Study 1100.1486, the FAS was used for analysis of all efficacy endpoints and the PPS was used only for a secondary analysis of the primary endpoint.

### Two Sets of Hypotheses: Testing Non-inferiority and Superiority

The null and alternative hypotheses for the primary efficacy endpoint  $H_{0,A}$  and  $H_{1,A}$  are

$$H_{0,A}: \pi_1 - \pi_0 \leq -0.10 \text{ vs. } H_{1,A}: \pi_1 - \pi_0 > -0.10$$

where  $\pi_1$  and  $\pi_0$  the population proportion of subjects with virologic response through Week 48 in the NVP XR and IR arms, respectively, and 10% is the non-inferiority margin.

A second null hypothesis  $H_{0,B}$  assumes that the XR formulation is not superior to the IR formulation in terms of virologic response proportion.

$$H_{0,B}: \pi_1 - \pi_0 \leq 0 \text{ vs. } H_{1,B}: \pi_1 - \pi_0 > 0$$

The null hypothesis  $H_{0,A}$  will be tested first.  $H_{0,B}$  will be tested if and only if  $H_{0,A}$  is rejected at the one-sided significance level  $\alpha = 0.025$ . This hierarchy preserves the overall alpha level.

For the test of the non-inferiority of the NVP XR to NVP IR with a 10% non-inferiority margin, a 95% confidence interval (CI) for the difference in the proportions of SVR between NVP XR and NVP IR treatment groups was constructed using Cochran's statistic, stratified by baseline HIV-1 viral load, and with continuity correction for the variance. If the lower 95% bound  $> -10\%$ , the non-inferiority of the NVP XR to NVP IR with respect to the SVR through Week 48 could be established.

### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

Disposition for randomized and treated subjects is presented in Table 1. In Study 1100.1486, 1068 patients entered the lead-in phase of the study and were considered as TS population, and 1013 HIV-1 infected and ARV-treatment naïve patients were randomized to one of the two treatments in a 1:1 ratio. Of these 1013 patients, 1011 were treated with blinded study drugs and were considered as the FAS population. Overall, 82% of the patients completed the Week 48 study and 17% of the patients were discontinued before Week 48. The most frequently reported reasons for discontinuing the study were "Adverse Events" (7%) and "Lack of Efficacy" (5%).

Demographics and baseline characteristics among all randomized subjects (n = 1013) in the TS population are presented in Table 2. Overall, demographics and baseline characteristics were similar between the two treatment groups. This population was mainly male (85%), Caucasian (75%), with a mean age 38 with a range of 18-71. Approximately half of the patients (50%) were from EU countries, 29% from North America, 11% from Latin America and 10% from Africa. At entry, this population had a mean weight 75.2 kg, mean CD4+ cell count 229

cells/mm<sup>3</sup>. Approximately 61% of the patients had screening HIV-1 RNA VL ≤100,000 copies/mL. 73% of the patients had HIV-1 subtype B, 6% had AIDS-defined illness prior to entry. Patients had approximately 15 days treatment with NVP IR in the lead-in phase.

**Table 1. 1100.1486: Randomization and Disposition Through Week 48\***

	NVP IR		NVP XR		Total	
	n	%	N	%	n	%
Enrolled					1626	
Treated with Lead-in Dose					1068	
Not randomized					55	
Randomized	508		505		1013	
Treated	506	100.0	505	100.0	1011	100.0
Completed 48 Week of Study	409	80.8	421	83.4	830	82.1
Discontinued	97	19.2	84	16.6	181	17.9
Death	3	0.6	1	0.2	4	0.4
Adverse Events	42	8.3	32	6.3	74	7.3
Lack of Efficacy	26	5.1	24	4.8	50	4.9
Non-compliance	9	1.8	6	1.2	15	1.5
Consent Withdrawn	9	1.8	4	0.8	13	1.3
Loss to follow-up	7	1.4	8	1.6	15	1.5
Pregnancy	0	0.0	6	1.2	6	0.6
Other	1	0.2	3	0.6	4	0.4

\*Source: FDA analysis.

**Table 2. 1100.1486: Subject Demographics and Baseline Characteristics\***

		NVP IR N=508		NVP XR N=505		Total N=1013	
<b>Age</b>	<b>Mean (SD)</b>	38.0	9.7	38.3	9.7	38.2	9.7
	<b>Median (range)</b>	37	18,68	38	19,71	38	18,71
		N	%	N	%	N	%
<b>Race</b>	<b>Asian</b>	13	2.56	15	2.97	28	2.76
	<b>White</b>	376	74.02	387	76.63	763	75.32
	<b>Black</b>	113	22.24	94	18.61	207	20.43
	<b>Other</b>	6	1.18	9	1.78	15	1.48
<b>Gender</b>	<b>Male</b>	433	85.24	431	85.35	864	85.29
	<b>Female</b>	75	14.76	74	14.65	149	14.71
<b>Region</b>	<b>Africa</b>	57	11.22	49	9.70	106	10.46
	<b>Europe</b>	252	49.61	257	50.89	509	50.25
	<b>Latin America</b>	49	9.65	58	11.49	107	10.56
	<b>North America</b>	150	29.53	141	27.92	291	28.73
<b>Ethnic</b>	<b>Hispanic</b>	109	21.46	115	22.77	224	22.11
	<b>Other</b>	399	78.54	390	77.23	789	77.89
	<b>Weight (Kg)</b>	N	505	504	1009		
	<b>Mean (SD)</b>	75.1	14.7	75.3	14.6	75.2	14.6
	<b>Median (range)</b>	73.3	38.0,127.4	74.8	42.0,140.2	74	38.0,140.2
<b>CD4+ cell count (cell/mm<sup>3</sup>)</b>	<b>N</b>	507		503		1010	
	<b>Mean (SD)</b>	227.6	85.9	229.6	81.4	228.6	83.7
	<b>Median (range)</b>	516.5	58.5,511	515	49.5,458.5	515.5	49.5,511
<b>HIV-1 RNA (copies/mL)</b>	<b>Mean (SD)</b>	4.68	0.65	4.67	0.69	4.68	0.67
	<b>Median (range)</b>	4.73	2.9,6.65	4.72	2.8,6.48	4.72	2.8,6.65
<b>HIV-1 RNA Stratum (copies/mL)</b>	<b>N</b>						
			%		%		%
	<b>≤100,000</b>	305	60.04	311	61.58	616	60.81
	<b>&gt;100,000</b>	203	39.96	194	38.42	397	39.19
<b>History of AIDS- defining illness</b>	<b>Yes</b>	26	5.1	30	5.9	56	5.5
<b>HIV-1 subtype B CDC Class</b>	<b>Yes</b>	360	70.9	379	75.0	739	73.0
	<b>Non-AIDS</b>	347	68.3	357	70.7	704	69.5
	<b>AIDS (A3,B3)</b>	141	27.8	130	25.7	271	26.8
	<b>AIDS (C1,C2,C3)</b>	20	3.9	18	3.6	38	3.8
	<b>Lead-in (days)</b>	<b>Mean (SD)</b>	14.8	2.3	14.9	2.7	14.7

Data Source: FDA analysis. \* Randomized subjects in TS population.

### 3.2.4 Efficacy Results

#### **Primary Efficacy endpoint**

For NVP XR labeling, the outcomes at Week 48 using Snapshot approach with LLOQ 50 copies/mL based on the Amplicor-corrected HIV-1 RNA assay profile are summarized in Table 3.

Table 4 provides proportion of subjects achieved sustained virologic response (SVR) through Week 48 (LLOQ 50 copies/mL) adjusting for the baseline HIV-1 RNA stratum. Two analysis algorithms (TLOVR or Snapshot) and two HIV RNA assay methods (TaqMan Only or Amplicor-corrected) were used for the computations. The estimated treatment difference (NVP XR-NVP IR) denoted by  $\Delta$  had a range from 3.0% to 4.9%, favoring the NVP XR group. The lower 95% CI bounds of  $\Delta$  were from -2.3% to -0.1% ( $>-10\%$ ), supporting the non-inferiority of NVP XR versus NVP IR, regardless of methods of estimation or HIV-1 RNA assay. Additionally, all p-values were greater than 0.05, indicating that the superiority of NVP XR versus NVP IR in 1100.1486 in the underlying SVRs could not be established.

Numerical variations in baseline HIV-1 RNA stratum-adjusted SVRs by four different approaches were observed. However, the treatment difference estimated by the TLOVR or Snapshot approach for the Amplicor-corrected assay was the same (4.9%).

**Table 3. Outcomes at Week 48 in Study 1100.1486**

	<b>NVP IR 200 BID N=506</b>	<b>NVP XR 400 QD N=505</b>
Virologic Success -HIV RNA $\leq$ 50 copies/mL	380 (75%)	405 (80%)
Virologic Failure#	67 (13%)	55 (11%)
No Virologic Data at 48 Window	59 (12%)	45 (9%)
<u>Reasons</u>		
Discontinued study/study drug due to AE or Death*	45 (9%)	33 (7%)
Discontinued study/study drug for Other Reasons**	13 (3%)	12 (2%)
Missing data during window but on study	1 (<1%)	

#Includes patients who changed OBT to new class or changed OBT not permitted per protocol or due to lack of efficacy prior to Week 48, subjects who discontinued prior to Week 48 for lack or loss of efficacy and patients who are  $\geq$  50 copies in the 48 week window.

\*Includes patients who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

\*\*Other includes: withdrew consent, loss to follow up, moved etc.

**Table 4. 1100.1486: SVR through Week 48 with LLOQ 50 copies/mL\***

Baseline RNA Copies/mL	NVP IR		NVP XR			Treatment Difference (%)**				
	r <sub>1</sub>	N <sub>1</sub>	100 ρ <sub>1</sub>	r <sub>2</sub>	N <sub>2</sub>	100 ρ <sub>2</sub>	Δ	95% CI		P-value
TLOVR (Amplicor-corrected)										
≤100,000	240	303	79.2	267	311	85.9	4.9	-0.1	10.0	0.307
>100,000	144	203	70.9	142	194	73.2				
TLOVR (TaqMan Only)										
≤100,000	237	303	78.2	256	311	82.3	3.5	-1.9	8.8	0.423
>100,000	131	203	64.5	130	194	67.0				
Snapshot (Amplicor-corrected)										
≤100,000	237	303	78.2	262	311	84.2	4.9	-0.2	10.1	0.310
>100,000	142	203	70.0	142	194	73.2				
Snapshot (TaqMan Only)										
≤100,000	234	303	77.2	252	311	81.0	3.0	-2.3	8.5	0.469
>100,000	127	203	62.6	125	194	64.4				

\*Data Source: FDA analysis on FAS population.

r<sub>k</sub>-# of responders, n<sub>k</sub>-sample size, ρ<sub>k</sub> = r<sub>k</sub>/n<sub>k</sub>, (k=1,2), Δ=100(ρ<sub>2</sub> - ρ<sub>1</sub>): treatment difference (NVP XR-NVP IR).

\*\* Δ and 95% CI – stratum-adjusted MH proportions and continuity-corrected variance.

### **Selected Secondary Efficacy endpoints**

The following selected secondary efficacy endpoints were evaluated by this reviewer:

- SVR through Week 48 based on Taqman assay for TLOVR and SNAPSHOT algorithms with LLOQ 400 copies/mL.
- Time to Loss of virologic Response through Week 48 using Cox Proportional Hazard models to estimate the hazard ratios (NVP XR vs. NVP IR).
- Change from baseline to Week 48 in CD4+ cell counts with LOCF for missing.

The SVR through Week 48 using TLOVR and SNAPSHOT algorithms with LLOQ 400 copies/mL based on Taqman assay results are summarized in Table 5. The treatment differences in SVR (NVP XR-NVP IR) are 4.2% for the TLOVR algorithm and 3.8% for the SNAPSHOT algorithm, favoring the NVP XR group. The treatment benefits in the NVP XR group may be associated with patients in the lower HIV-1 RNA stratum (≤100,000 copies/mL). Compared the SVR results with LLOQ 50 copies/mL, the treatment differences in SVR appear to be robust, and the SVR with LLOQ 400 copies/mL for each subcategory is numerically greater.

**Table 5. 1100.1486: SVR through Week 48 with LLOQ 400 copies/mL\***

Baseline RNA Copies/mL	NVP IR						NVP XR				Treatment Difference (%)**		
	$r_1$	$N_1$	$100 \rho_1$	$r_2$	$N_2$	$100 \rho_2$	$\Delta$	95% CI		P-value			
TLOVR (TaqMan Only)													
$\leq 100,000$	244	303	80.5	273	311	87.8	4.2	-0.6	9.0	0.339			
$> 100,000$	155	203	76.4	147	194	75.8							
Snapshot (TaqMan Only)													
$\leq 100,000$	244	303	80.5	271	311	87.1	3.8	-1.1	8.6	0.368			
$> 100,000$	155	203	76.4	147	194	75.8							

\*Data Source: FDA analysis on FAS population.

$r_k$ -# of responders,  $n_k$ -sample size,  $\rho_k = r_k/n_k$ , ( $k=1,2$ ),  $\Delta=100(\rho_2 - \rho_1)$ : treatment difference (NVP XR-NVP IR).

\*\*  $\Delta$  and 95% CI – stratum-adjusted MH proportions and continuity-corrected variance.

Time to loss of virologic response was conducted to estimate hazard ratios using Cox models based on the TLOVR algorithm with LLOQ 50 copies/mL, and results are summarized in Table 6. The hazard ratios (NVP XR versus NP IR) were similar: 81% (p 0.08), and 85% (p 0.12) respectively for Amplicor-corrected assay and the TaqMan-only assay profile. For data obtained using Amplicor-corrected assay, the patients in the NVP XR group were at 81% risk of losing virologic response than those in the NVP IR group. The Cox model assumes that the two hazard rates for the two treatment groups are proportional over time. Please note that probability of virologic failure (VF)-free is probability of virologic response. Reviewer’s results in Table 6 are similar to those from the sponsors’ in Table 3.2.1.2: 1 (Summary-cli-efficacy.pdf).

In addition, Kaplan-Meier approach was used for the graphical presentation. Figures 1 and 2 display virologic failure (VF)-free survival curves stratified by treatment arm and baseline HIV-1 RNA stratum respectively for the two assay profiles. In the two subgroups with baseline HIV-1 RNA  $\leq 100,000$  copies/mL, patients in the NVP XR group were more likely to have virologic response than the NVP IR group through Week 48. In the two groups with baseline HIV-1 RNA  $> 100,000$  copies/mL, however, the difference in virologic response could be ignored.

**Table 6. 1100.1486: Estimated Hazard Ratio of Losing Virologic Response Using Cox Model\***

		df	B	Se( $\beta$ )	Chi-sq	Hazard Ratio	p-value
Amplicor- Corrected	NVR XR	1	-0.215	0.122	3.122	0.806	0.0773
	Low RNA	1	-0.476	0.121	15.432	0.621	<.0001
TaqMan	NVR XR	1	-0.177	0.114	2.413	0.837	0.1204
	Low RNA	1	-0.569	0.114	24.949	0.566	<.0001

\*Data Source: FDA analysis on FAS population, LLOQ=50 copies/mL using TLOVR algorithm.

Low RNA- Baseline HIV-1 RNA  $\leq 100,000$  copies/mL, df-degree of freedom,  $\beta$ - MLE of parameter.

Observed and estimated mean change from baseline to Week 48 in CD4+ are provided in Table 7. Week 48 CD4+ was the CD4+ value in the interval of Week 44 to Week 52. Missing in CD4+ was imputed using the LOCF with or without restrictions of 28 days (4 weeks). The estimated mean change from baseline to Week 48 in CD4+ was 191 and 206 cells/mm<sup>3</sup> respectively in the NVP IR and NVP XR groups, based on a random-effect model controlling for the baseline HIV-1 RNA stratum. The observed mean change from baseline to Week 48 in CD4+ was 185 and 199 cells/mm<sup>3</sup> respectively in the NVP IR and NVP XR groups. The mean difference between LOCF with and without restrictions was about 4-5 cells/mm<sup>3</sup>. The protocol defined time point for LOCF was ‘visit 3’.

**Table 7. Observed and Estimated Mean Change from Baseline to Week 48 in CD4+\***

<b>Part I: Observed CD4+</b>						
	n	mean	Std	median	minimum	maximum
1. ΔCD4+ at Week 48: LOCF with restrictions <sup>1</sup>						
NVP IR	490	185	137	166	-138	966
NVP XR	489	199	142	176	-99	952
Total	979	192	140	170	-138	966
2. ΔCD4+ at Week 48: LOCF with no restrictions						
NVP IR	504	181	138	162	-138	966
NVP XR	503	194	144	171	-99	952
Total	1007	188	141	167	-138	966
<b>Part II: Estimated ΔCD4+ at Week 48</b>						
	N	β	Se(β)	N	β	Se(β)
	LOCF with restrictions <sup>1,2</sup>			LOCF with no restrictions <sup>2</sup>		
NVP IR	490	191	6.42	504	187	6.39
NVP XR	489	206	6.48	503	201	6.44

\*Data Source: FDA analysis on FAS population, ΔCD4+: change from baseline in CD4+.

1. LOCF for those with last day of non missing CD4+ >28 days since Day 1.

2. Random effect modeling adjusting for baseline HIV 1 RNA stratum.

Notations for Figures 1 and 2:

L- Baseline HIV-1 VL≤100,000 c/mL, H- Baseline HIV-1 VL>100,000 c/mL.

TLOVR/LLOQ=50/Ampl-corr

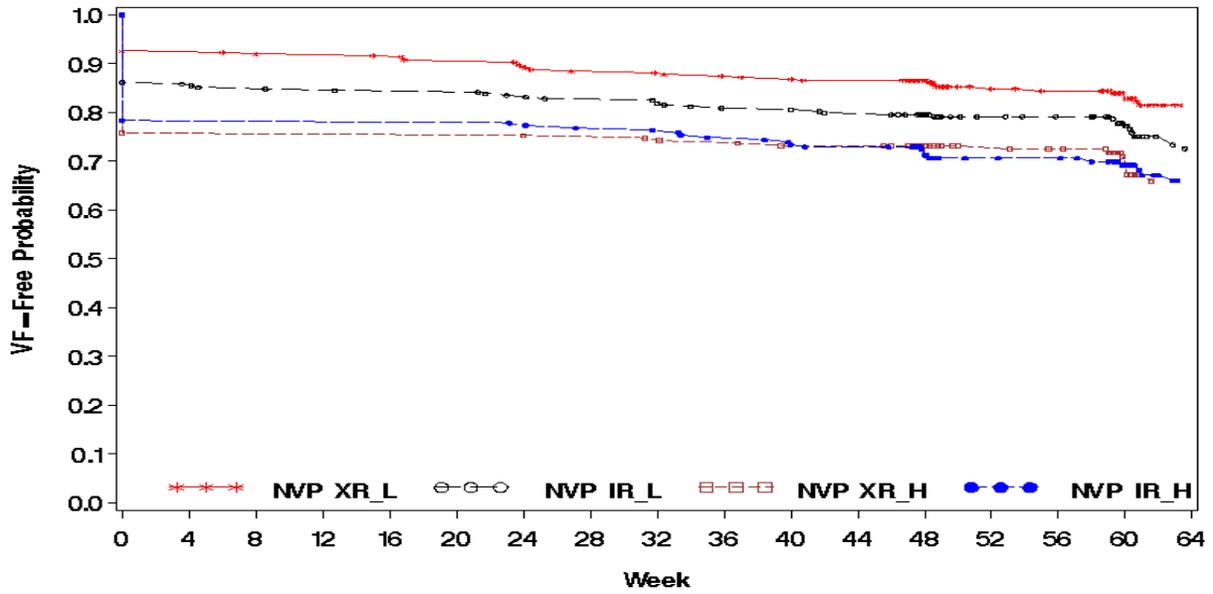


Figure 1: 1100.1486: K-M (TLOVR, LLOQ 50 copies/mL, AmpliCor-corrected Assay)

TLOVR/LLOQ=50/TaqMan

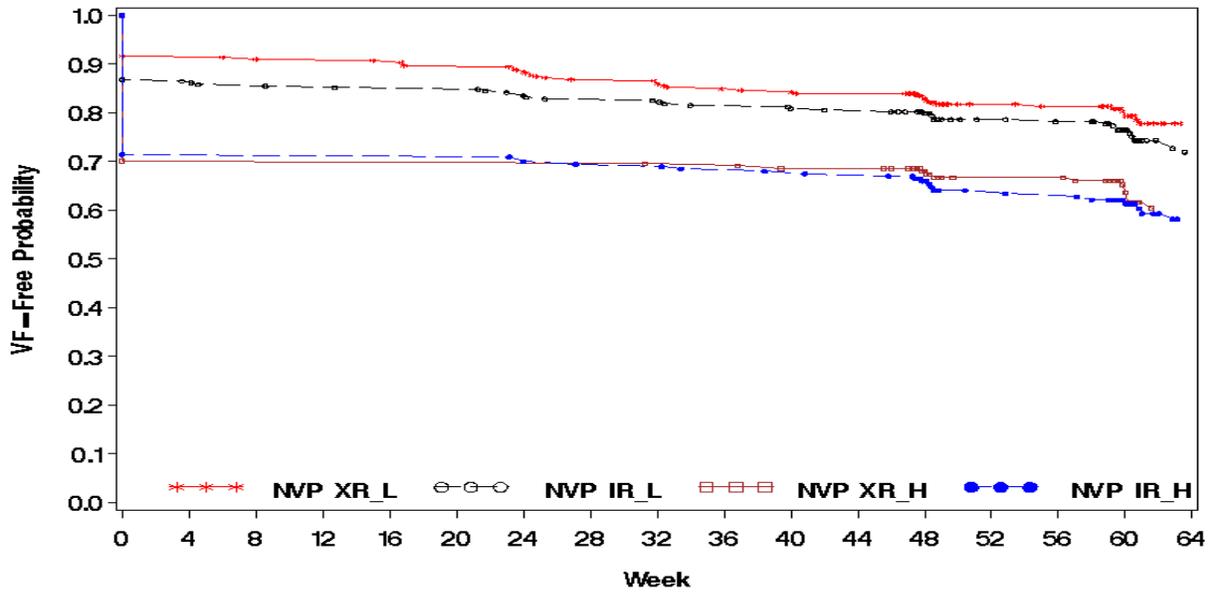


Figure 2: 1100.1486: K-M (LLOQ 50 copies/mL, TaqMan Assay)

### 3.3 Evaluation of Safety

Please refer to medical officer Dr. Peter Miele’s review for the evaluation of NVP safety.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This reviewer verified sponsor’s results on subgroup populations regarding the primary efficacy endpoint, defined as SVR at Week 48 with LLOQ 50 copies/mL based on snapshot approach and Amplicor-corrected assay profile. No significant associations were found for selected key baseline demographic and disease characteristics.

### 4.1 Gender, Race, Age, Ethnic and Geographic Region

The observed SVRs at Week 48 (LLOQ 50 copies/mL) across age ( $\leq 40$ , 41-55,  $> 55$ ), gender, race (white, black, other), Hispanic or not, and geographic region (Africa, Europe, Latin America, North American) are summarized in Table 8. Except for ‘Other Racial’ group with sample sizes are relatively small, all observed treatment differences (NVP IR-NVP XR) in SVR were -9% to -2%, indicating a numerical benefit in favor of the NVP XR group.

**Table 8. Subgroup Analyses of Observed SVR at Week 48\***

Subgroup	NVP IR			NVP XR			Difference (%)	
	$r_1$	$n_1$	$100 \rho_1$	$r_2$	$n_2$	$100 \rho_2$	$100x (\rho_2 - \rho_1)$	
<b>Age</b>	<b><math>\leq 40</math></b>	233	314	74.2	236	300	78.7	4.5
	<b>41-55</b>	128	165	77.6	150	181	82.9	5.3
	<b><math>&gt; 55</math></b>	19	27	70.4	19	24	79.2	8.8
<b>Female</b>		54	75	72.0	55	74	74.3	2.3
	<b>Male</b>	326	431	75.6	350	431	81.2	5.6
<b>White</b>		281	374	75.1	317	387	81.9	6.8
	<b>Black</b>	84	113	74.3	73	94	77.7	3.3
	<b>Other</b>	15	19	79.0	15	24	62.5	-16.5
<b>Hispanic</b>		80	108	74.1	93	115	80.9	6.8
	<b>Non-Hispanic</b>	300	398	75.4	312	390	80.0	4.6
<b>Africa</b>		45	57	79.0	40	49	81.6	2.7
	<b>Europe</b>	183	252	72.6	199	257	77.4	4.8
<b>Latin-America</b>	39	49	79.6	50	58	86.2	6.6	
<b>North-America</b>	113	148	76.4	116	141	82.3	5.9	
<b>Overall</b>	380	506	75.1	405	505	80.2	5.1	

\*Data Source: FDA analysis in FAS population. SVR LLOQ 50 copies/mL, snapshot, Amplicor corrected assay.

\*\*  $r_k$ -# of responders,  $n_k$ -sample size,  $\rho_k = r_k/n_k$ , ( $k=1,2$ ),  $\rho_2 - \rho_1$ :treatment difference (NVP XR-NVP IR).

Table 9 lists the estimated treatment differences in SVRs (denoted by CMH\_d) by the underlying subgroups. The CMH\_d and 95% CI were obtained adjusting for the baseline HIV-1 RNA stratum. Except for the other racial subgroup, all treatment differences (NVP IR-NVP XR) adjusting for the baseline HIV-1 RNA stratum showed a numerical benefit (2% to 9%) in favor of NVP XR group. The treatment by each of the baseline characteristics was not statistically significant different from zero, at type I error of 0.2 level using the Chi-square test on the treatment with interaction term(s) in hierarchical logistic regression models.

**Table 9. Subgroup Analyses of Treatment Difference in Week 48 SVR\***

	CMH d	Se	95% CI		Wald t	p-value	p-value <sub>2</sub>
<b>Age</b>							
<b>≤40</b>	3.6	3.4	-3.1	10.2	1.050	0.484	0.819
<b>41-55</b>	5.4	4.3	-3.1	13.9	1.241	0.432	
<b>&gt;55</b>	9.3	13.3	-16.7	35.3	0.699	0.612	
<b>Female</b>	2.3	7.4	-12.2	16.8	0.310	0.809	0.610
<b>Male</b>	5.4	2.8	-0.1	10.8	1.926	0.305	
<b>White</b>	6.4	3.0	0.6	12.3	2.175	0.274	0.323
<b>Black</b>	3.3	6.1	-8.6	15.2	0.544	0.683	
<b>Other</b>	-4.9	15.7	-35.7	25.9	-0.311	0.808	
<b>Hispanic</b>	6.9	5.6	-4.1	17.8	1.224	0.436	0.701
<b>Non-Hispanic</b>	4.4	3.0	-1.4	10.2	1.495	0.375	
<b>Africa</b>	2.7	8.1	-13.0	18.5	0.340	0.792	0.946
<b>Europe</b>	4.5	3.8	-2.9	12.0	1.192	0.444	
<b>Latin-America</b>	8.2	7.4	-6.3	22.8	1.108	0.467	
<b>North-America</b>	5.7	4.8	-3.7	15.1	1.189	0.445	
<b>Overall</b>	4.9	2.6	-0.2	10.0	1.890	0.310	

\*Data Source: FDA analysis of the primary efficacy endpoint in FAS population. SVR (%)-snapshot, LLOQ=50 copies/mL, Amplicor-corrected assay.

CMH\_d-treatment difference (NVP XR-NVP IR) adjusting for baseline HIV-1 RNA strata; se-standard error; p-value: for testing treatment difference by the Wald-t test;

p-value<sub>2</sub> for testing treatment by covariate interaction using the Chi-square test in hierarchical logistic regression models.

## 4.2 Other Special/Subgroup Populations

Sample size, frequency of virologic response, observed SVR, and treatment differences (NVP IR-NVP XR) in SVR by baseline HIV-1 RNA stratum and baseline CD4+ cell count (≤200, >200 cells/mm<sup>3</sup>) are provided in Table 10. All observed treatment differences (NVP IR-NVP XR) showed a numerical benefit in favor of NVP XR group. Patients with baseline HIV-1 RNA

$\leq 100,000$  copies/mL appeared to have greater SVRs than those with baseline HIV-1 RNA  $> 100,000$  copies/mL. On the contrary, patients with baseline CD4+ cell count  $\leq 200$  cells/mm<sup>3</sup> appeared to have lesser SVRs than those with baseline CD4+ cell count  $> 200$  cells/mm<sup>3</sup>.

The treatment by baseline HIV-1 RNA stratum or CD4+ stratum was not statistically significant different from zero, at type I error of 0.2 level.

**Table 10. 1100.1486: Subgroup Analyses of Virological Responders at Week 48 (Snapshot)\***

Baseline	NVP IR			NVP XR			Difference 100x ( $\rho_2 - \rho_1$ )
	$r_1$	$n_1$	100 $\rho_1$	$r_2$	$n_2$	100 $\rho_2$	
<b>HIV-1 VL (copies/mL)</b>							
$\leq 100,000$	237	303	78.22	264	311	84.89	6.67
$> 100,000$	143	203	70.44	141	194	72.68	2.24
Testing interaction with treatment: $\text{diff}(\Delta) = 4.4\%$ , $\text{se} = 5.5\%$ , $t = 0.806$ , $p = 0.420$							
<b>CD4+ (cells/mm<sup>3</sup>)</b>							
$\leq 200$	144	200	72.00	135	179	75.42	3.42
$> 200$	234	305	76.72	267	324	82.41	5.69
Testing interaction with treatment: $\text{diff}(\Delta) = -2.3\%$ , $\text{se} = 5.5\%$ , $t = 0.409$ , $p = 0.683$							

\*Data Source: FDA analysis of the primary efficacy endpoint in FAS population. SVR-snapshot, LLOQ=50 copies/mL, Amplicor-corrected assay.

\*\*  $r_k$ -# of responders,  $n_k$ -sample size,  $\rho_k = r_k/n_k$ , ( $k=1,2$ ),  $\rho_2 - \rho_1$ : treatment difference (NVP XR-NVP IR).

### 4.3 Comparisons of Different Estimation Methodologies and HIV-1 RNA Assay Profiles via Agreement Statistics

Numerical variations in baseline HIV-1 RNA stratum-adjusted SVRs by four different approaches were observed. There are 26 discordant pairs (2.6%) using the TLOVR and snapshot approaches with LLOQ 50 copies/mL, based on the Amplicor-corrected assay profile even though the treatment differences in SVR (NVP XR-NVP IR) are similar (4.9%). Hence, this reviewer evaluated agreements, concordance and discordance, by a detailed analysis of the FAS population for six permutations with four differing methods: (TLOVR and Snapshot) x (TaqMan and Amplicor-corrected assay), with LLOQ 50 copies/mL.

Table 11 summarizes the results. Least and most discordance findings were:

- The least discordance - found in Scenario #1, the comparison of SVR between TLOVR and SNAPSHOT using Amplicor-corrected assay profile, where Scenario #1 resulted in 26 discordant pairs (i.e., 2.5% discordant pairs).
- The most discordance - found in Scenario #2, the comparison of SVR involving SNAPSHOT between Amplicor-corrected assay profile and TaqMan assay, where Scenario #2 resulted 83 discordant pairs (i.e., 8.2% discordant pairs).

Using the Cohen's Kappa with Fleiss's Equally Arbitrary Guidelines criteria<sup>2,3,4</sup>, where Kappa<40% is an indication of poor agreement and Kappa>75% is an indication of excellent agreement, all six scenarios have excellent agreement. Thus, we conclude that the HIV-1 RNA VL assay profiles and methods of estimation did not have significant impact on the SVR.

**Table 11. 1100.1486: Concordance and Discordance in SVR at Week 48\***

#	V48_50	V48_T50	V48_50Q	V48_T50Q	COUNT	%	Kappa Se	Wald-t	p-value
1	N	N			210	20.77	0.9252	3.8462	0.0499
	N	Y			18	1.78	0.0145		
	Y	N			8	0.79			
	Y	Y			775	76.66			
2	N		N		209	20.67	0.7803	24.3976	<0.0001
	N		Y		19	1.88	0.0228		
	Y		N		64	6.33			
	Y		Y		719	71.12			
3	N			N	207	20.47	0.8076	11.8451	0.0006
	N			Y	21	2.08	0.0218		
	Y			N	50	4.95			
	Y			Y	733	72.50			
4		N	N		206	20.38	0.7884	38.2911	<0.0001
		N	Y		12	1.19	0.0225		
		Y	N		67	6.63			
		Y	Y		726	71.81			
5		N		N	207	20.47	0.8325	24.9344	<0.0001
		N		Y	11	1.09	0.0206		
		Y		N	50	4.95			
		Y		Y	743	73.49			
6			N	N	242	23.94	0.8824	5.5652	0.0183
			N	Y	31	3.07	0.0169		
			Y	N	15	1.48			
			Y	Y	723	71.51			

\*Data Source: FDA analysis on FAS population. 'Y' – responder, 'N' non-responder.

V48\_50 - SVR using Amplicor-corrected assay & Snapshot Approach;  
V48\_T50 - SVR using Amplicor-corrected assay & TLOVR Approach;  
V48\_50Q- SVR using TaqMan assay & Snapshot Approach; and  
V48\_T50Q - SVR using TaqMan assay & TLOVR Approach.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

BIPI submitted the antiviral efficacy and safety data from one principal clinical trial 1100.1486 and one supportive trial 1100.1526, both were randomized, controlled, non-inferiority Phase III trials in adult patients with HIV-1 infection. For the statistical evaluation of the supportive trial 1100.1526, please refer to Lan Zeng's review for details.

There is no major statistical issue in the study design and analysis for the Phase III trial 1100.1486. Per statistical review of efficacy in 1100.1486, we have the following results.

The pivotal trial 1100.1486 was conducted double-blinded in treatment-naïve patients. 1011 patients were randomized and treated with 400 mg QD NVP XR formulation or the 200 mg BID NVP IR, both in combination with Truvada<sup>®</sup> (emtricitabine and tenofovir disoproxil fumarate) QD after a 2-week lead-in phase treatment with NVP IR 200 mg QD. After 48 week treatment, 405/505 (80.2%) of NVP XR patients and 380/506 (75.1%) of NVP IR patients achieved HIV-1 RNA < 50 copies/mL (virologic response), with a difference of 4.9% with 95% CI: (-0.2%, 10.1%) adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL). In addition, mean change from baseline in CD4+ cell count adjusting for baseline HIV-1 viral load stratum was 206 cells/mm<sup>3</sup> and 191 cells/mm<sup>3</sup> for the groups receiving NVP XR and NVP IR respectively. The virologic responses at Week 48 were obtained using snapshot algorithm on HIV-1 RNA via Amplicor-corrected virologic assay (snapshot algorithm/Amplicor-corrected HIV assay).

- The lower bounds of the difference was greater than the pre-specified non-inferiority margins: -10%, demonstrating the non-inferiority of NVP XR to NVP IR treatment among ARV-treatment naïve HIV-1 infected patients in 1100.1486.
- The non-inferiority of NVP XR to NVP IR in 1100.1486 was robust and numerically consistent regardless of HIV-1 RNA viral load assay profile and algorithm (TaqMan only or 'Amplicor-corrected'), algorithms for the estimation of SVR (the TLOVR or Snapshot approach), and the level of lower limit of quantification (LLOQ 50 or 400 copies/mL). This reviewer conducted a sensitivity analysis to evaluate the concordant and discordant pairs in the SVRs by six scenarios using Cohen's Kappa statistic with Fleiss's Equally Arbitrary Guidelines criteria. All six scenarios showed excellent agreement. It has been concluded the HIV-1 RNA VL assay profiles and methods of estimation did not have significant impact on the estimation of the SVRs.
- Subgroup analysis on Week 48 virologic response with respect to age, gender, race, ethnicity, and geographic region adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL) showed numerical benefit in the NVP XR group versus NVP IR group with a range of 2.3% to 9.3%. At type I of 0.20 level, treatment by age, gender, race, ethnic, geographic region interactions were not statistically significant different from zero. Likewise, treatment by baseline HIV-1 RNA strata or baseline CD4+ ( $\leq$  or  $>$ 200 cells/mm<sup>3</sup>) were not statistically significant from zero.

## 5.2 Conclusions and Recommendations

BIPI's key efficacy results in the two trials can be replicated by the statistical reviewers. BIPI concluded that treatment with NVP XR 400 mg QD was non-inferior to treatment with NVP IR 200 mg BID. Based on the statistical evaluation of efficacy data in 1100.1486 and 1100.1526, the statistical reviewers concur with BIPI's conclusions.

## 6 APPENDICES

### 6.1 References

1. Snapshot document final 032910.doc. DAVP, 2010.
2. Carletta, Jean. (1996). Assessing agreement on classification tasks: The kappa statistic. *Computational Linguistics*, 22(2), pp. 249–254.
3. Fleiss, J.L. (1981). *Statistical methods for rates and proportions* (2nd ed.). New York: John Wiley.
4. Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E., and Uryniak, T.J. (1989). *Categorical Data Analysis*. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.
5. Daniel Podzamczar, et al. Safety of Switching Nevirapine Twice Daily to Nevirapine Once Daily in Virologically Suppressed Patients. *J. Acquir Immune Defic Syndr.* 2009 April 1; 50(4), Number 4.
6. Greg Soon, Testing Interaction for Independent Covariates Using Microsoft Excel. 2002.

## **7 SIGNATURES/DISTRIBUTION LIST (Optional)**

Primary Statistical Reviewer: Susan Zhou, Ph.D.

Date: March 4, 2011

Statistical Team Leader: Greg Soon, Ph.D.

Biometrics Division Director: Mohammad Huque, Ph.D.

cc:

Project Manager: Amalia Himaya

Medical Officer: Peter Miele, M.D.

Medical Team Leader: Linda Lewis, M.D.

Primary Statistical Reviewer: Susan Zhou, Ph.D.

Primary Statistical Reviewer: Lan Zeng

Statistical Team Leader: Greg Soon, Ph.D.

Biometrics Division Director: Mohammad Huque, Ph.D.

Biometrics Division Deputy Director: Daphne Lin, Ph.D.

Office of Biostatistics: Lillian Patrician

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

/s/  
-----

SUSAN Y ZHOU  
03/04/2011

GUOXING SOON  
03/04/2011



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA Serial Number:** 201,152

**Drug Name:** Viramune<sup>®</sup> XR<sup>™</sup> (nevirapine) extended-release tablets

**Indication(s):** Treatment of HIV-1 infection, for use in combination with other ART agents

**Applicant:** Boehringer Ingelheim, Inc.

**Date(s):** Submitted: June 3, 2010  
Mid-cycle GAM: October 27, 2010  
PDUFA date: March 3, 2011

**Review Priority:** Standard

**Biometrics Division:** Division IV

**Statistical Reviewer:** Lan Zeng (HFD-725)

**Concurring Reviewers:** Greg Soon, Ph.D. (HFD-725)

**Medical Division:** DAVP

**Clinical Team:** Peter Miele, M.D. (HFD-530)

**Project Manager:** Amalia Himaya (HFD-530)

**Keywords:** Non-inferiority, Taqman and Amplicor-corrected profile, Sustained Virologic Response, TLOVR and SNAPSHOT.

# Table of Contents

<b>1. EXECUTIVE SUMMARY</b> .....	<b>4</b>
<b>2. INTRODUCTION</b> .....	<b>6</b>
2.1 OVERVIEW .....	6
2.2 DATA SOURCES .....	6
<b>3. STATISTICAL EVALUATION</b> .....	<b>7</b>
3.1 DATA AND ANALYSIS QUALITY .....	7
3.2 EVALUATION OF EFFICACY .....	7
3.2.1 STUDY DESIGN AND ENDPOINTS .....	7
3.2.2 STATISTICAL METHODOLOGIES .....	8
3.2.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS .....	10
3.2.4 EFFICACY RESULTS .....	13
3.2.5 ADDITIONAL ANALYSES.....	16
3.3 EVALUATION OF SAFETY.....	18
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS</b> .....	<b>18</b>
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION .....	18
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	20
<b>5. SUMMARY AND CONCLUSIONS</b> .....	<b>23</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	23
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	24

## LIST OF TABLES

Table 1 Patients Disposition up to Week 24.....	10
Table 2 Demographic Data FAS.....	11
Table 3 Baseline characteristics FAS .....	12
Table 4 Study Outcome through Week 24 with LLOQ 50 copies/mL - TLOVR - FAS .....	13
Table 5 Analysis of Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL (No. with response/Total No. [%]).....	14
Table 6 Summary of HIV-1 viral load (copies/mL) and Change from Baseline by Visit - FAS - TaqMan.....	15
Table 7 Summary of CD4+ Count (cells/mm <sup>3</sup> ) and Change from Baseline by Visit - FAS .....	16
Table 8 Comparison of TaqMan assay and Amplicor-corrected Assay in Defining Sustained Virologic Response at Week 24.....	17
Table 9 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Demographics (No. with response/Total No.[%]) FAS - Amplicor-corrected.....	19
Table 10 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Demographics (No. with response/Total No.[%]) FAS - TaqMan.....	19
Table 11 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by background ARV therapy (No. with response/Total No.[%]) - FAS .....	20
Table 12 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Characteristics (No. with response/Total No.[%]) FAS -Amplicor-corrected .....	21
Table 13 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Characteristics (No. with response/Total No.[%]) FAS - TaqMan .....	22

## 1. EXECUTIVE SUMMARY

*This is an integrated executive summary based on statistical review of Study 1100.1486 and Study 1100.1526.*

Boehringer Ingelheim Pharmaceutical Inc. (BIPI) submitted NDA 201,152 to apply for the approval of 400 mg QD nevirapine extended release formulation (VIRAMUNE XR, NVP XR) in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. Consideration of approval for this NDA is based on the antiviral efficacy and safety from one principal clinical trial 1100.1486 and one supportive trial 1100.1526, both were randomized, controlled, non-inferiority Phase III trials in adult patients with HIV-1 infection. The 200 mg BID nevirapine 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 pivotal trial 1100.1486 was conducted double-blinded in treatment-naïve patients. 1013 patients were randomized in a 1:1 ratio to the 400 mg QD NVP XR formulation or the 200 mg BID NVP IR, both in combination with Truvada<sup>®</sup> (emtricitabine and tenofovir disoproxil fumarate) QD after a 2-week lead-in phase treatment with NVP IR 200 mg QD. After 48 week treatment among 1011 patients, 405/505 (80.2%) of NVP XR patients and 380/506 (75.1%) of NVP IR patients achieved HIV-1 RNA < 50 copies/mL (virologic response), with a difference of 4.9% with 95% CI: (-0.2%, 10.1%) adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL). In addition, mean change from baseline in CD4+ cell count adjusting for baseline HIV-1 viral load stratum was 206 cells/mm<sup>3</sup> and 191 cells/mm<sup>3</sup> for the groups receiving NVP XR and NVP IR respectively. The virologic responses at Week 48 were obtained using snapshot algorithm on HIV-1 RNA via Amplicor-corrected virologic assay (snapshot algorithm/Amplicor-corrected HIV assay).

- The lower bounds of the difference was greater than the pre-specified non-inferiority margins: -10%, demonstrating the non-inferiority of NVP XR to NVP IR treatment among ARV-treatment naïve HIV-1 infected patients in 1100.1486.
- The non-inferiority of NVP XR to NVP IR in 1100.1486 were consistent regardless of HIV-1 RNA viral load assay and algorithm (TaqMan only or ‘Amplicor-corrected’), algorithms for the estimation of sustained virologic responses (the TLOVR algorithm or Snapshot approach), and different analysis data sets.
- Subgroup analysis on Week 48 virologic response with respect to age, gender, race, ethnicity, and geographic region adjusting for the baseline HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL) showed slightly numerical benefit in the NVP XR group versus NVP IR group with a range of 2.3% to 9.3%. At 0.20 significance level, treatment by age, gender, race, geographic region interactions were not statistically significant different from zero. Likewise, treatment by baseline HIV-1 RNA strata or baseline CD4+ ( $\leq$  or  $>$ 200 cells/mm<sup>3</sup>) were not statistically significant from zero.

The supportive trial 1100.1526 was conducted in an open-label manner in treatment-experienced patients. A total of 443 patients already on an antiviral regimen containing 200 mg BID NVP IR with HIV-1 RNA < 50 copies/mL were randomized in a 2:1 ratio to either switch to the 400 mg QD NVP XR formulation or continue on the 200 mg BID NVP IR, while remaining on their

previous background therapy. According to the snapshot algorithm and Amplicor-corrected HIV assay, 281/295 (95.3%) of NVP XR patients and 139/148 (93.9%) of NVP IR patients had maintained virologic suppression (HIV-1 RNA < 50 copies/mL) by Week 24, with a difference of 1.3% in favor of NVP XR (95% CI: -3.5%, 6.1%) adjusting for the baseline background therapy.

- The lower bound of the treatment difference was greater than the pre-specified non-inferiority margin -12%, demonstrating the non-inferiority of NVP XR to NVP IR treatment among ARV-treatment experienced HIV-1 infected patients in 1100.1526.
- The non-inferiority of NVP XR to NVP IR in 1100.1526 were consistent regardless of HIV-1 RNA viral load assay and algorithm (TaqMan only or 'Amplicor-corrected'), algorithms for the estimation of sustained virologic responses (the TLOVR algorithm or Snapshot approach), and different analysis data sets.
- Subgroup analysis on sustained virologic response (HIV-1 RNA < 50 copies/mL) by Week 24 with respect to baseline demographics (age, gender, race, and geographic region) or clinical characteristics (CD4+ cell count, CDC class, HIV-1 baseline viral load, nevirapine as first highly active antiretroviral therapy regimen, duration of previous NVP IR treatment, and type of previous background therapy) showed numerically similarities between the NVP XR and NVP IR groups. There is no apparent relationship between the proportion of sustained virologic responders at Week 24 and any baseline demographics or clinical characteristic.
- Due to the open-label design feature of Study 1100.1526, interpretation of the key underlying efficacy results is limited by the facts that patients were already on a NVP IR BID regimen and were virologically suppressed for at least 18 weeks prior to enrollment, and only selected specimens were assayed using both virologic methods (TaqMan and Amplicor) as a result of protocol change.

BIPI's key efficacy results in the two trials can be replicated by the statistical reviewers. BIPI concluded that treatment with NVP XR 400 mg QD was non-inferior to treatment with NVP IR 200 mg BID. Based on the statistical evaluation of efficacy data in Studies 1100.1486 and 1100.1526, the statistical reviewers concur with BIPI's conclusions.

This reviewer conducted the statistical review of efficacy data in Study 1100.1526. The statistical review of efficacy in Study 1100.1486 was performed by Susan Zhou. Please refer to her review document for details.

## 2. INTRODUCTION

### 2.1 Overview

Nevirapine is a non-nucleoside reverse transcriptase inhibitor developed by Boehringer Ingelheim Pharmaceuticals, Inc. for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1(HIV-1) infection. Nevirapine IR (NVP IR, immediate release formulation marketed as VIRAMUNE) tablets received first marketing authorization in the US in June 1996. An oral suspension formulation was approved in 1998. Subsequent approvals for the tablets and the oral suspension have been obtained in over 100 countries. Nevirapine IR is administered as once daily (QD) 200 mg from Day 1 to 14 followed by 200 mg twice daily (BID). In order to improve treatment convenience and thus potentially adherence, the sponsor has developed an extended release oral tablet formulation, nevirapine XR (NVP XR, extended release formulation), to be administered as a once daily (QD) 400 mg regimen. The current NDA seeks to register nevirapine XR tablet (VIRAMUNE XR) in the same indication as nevirapine IR tablet (VIRAMUNE) for combination antiretroviral treatment of HIV-1 infection.

The sponsor's clinical development program of nevirapine XR included 3 Phase I studies (1100.1484, 1100.1485, and 1100.1489) and 2 Phase III studies (1100.1486 and 1100.1526). The Phase I studies were conducted to determine the intestinal absorption of nevirapine, the PK profile, and the optimal formulation. The 2 Phase III studies were conducted to support clinical efficacy of nevirapine XR tablets in two patient treatment settings, the treatment-naïve patients (1100.1486) and the treatment-experienced patients to be switched from the nevirapine IR BID dosing regimen to the nevirapine XR QD dosing (1100.1526). Study 1100.1486 was a randomized, double-blind non-inferiority study assessing efficacy and safety of nevirapine XR tablets administered once daily (QD) versus nevirapine IR administered twice daily (BID) and on a fixed background ARV regimen of tenofovir and emtricitabine (Truvada®) in treatment-naïve, HIV-1 infected patients. Study 1100.1526 was a randomized, open-label non-inferiority study assessing the efficacy and safety of nevirapine XR in patients who transitioned from nevirapine IR administered BID to nevirapine XR tablets administered QD.

The pivotal trial, Study 1100.1486, is reviewed by Susan Zhou. The current review will describe Study 1100.1526 and evaluate efficacy data from this supportive trial.

### 2.2 Data Sources

Datasets and all modules containing clinical study reports were submitted electronically. The full electronic path according to the CDER EDR naming convention is as follows:

\\Cdsesub1\evsprod\NDA201152\

### 3. STATISTICAL EVALUATION

This section presents the detailed review of Study 1100.1526, entitled “*An open label, phase IIIb, randomized parallel group study to assess the efficacy and safety of switching HIV-1 infected patients successfully treated with a Nevirapine IR based regimen to Nevirapine XR 400 mg QD or remaining on Nevirapine IR 200 mg BID based regimen*”.

#### 3.1 Data and Analysis Quality

The data sets generally represented the data described in the study reports. However, one key variable ‘USUBJID’ (Unique Subject Identifier) was constructed differently in different datasets and couldn’t be used to link various datasets without further manipulation. For instance, USUBJID was defined as a character variable with length of 20 in “BASCO.XPT” but as a character variable with length of 25 in “ADAMEFF.XPT”. Data manipulation is required in order to merge these two datasets together.

The analyses performed by the sponsor are generally acceptable.

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Study Design and Endpoints

Study 1100.1526 was an open-label trial designed to assess the efficacy and safety of nevirapine XR in patients who transitioned from nevirapine IR administered BID to nevirapine XR tablets administered QD. Eligible patients had confirmed HIV-1 RNA viral <50 copies/mL at screening and also had received at least 18 weeks of nevirapine IR BID with 1 of the 3 possible background therapies (3TC/ABC [Kivexa®/ Epzicom™], FTC/TDF [Truvada®] or 3TC/AZT [Combivir®]). After screening, patients were randomized (stratified by background therapy) in a 2:1 ratio to either switch to the 400 mg QD nevirapine XR formulation or continue on the 200 mg BID nevirapine IR formulation, while remaining on their previous background therapy. Patients had scheduled visits on Weeks 0, 2, 4, 8, 12, 24, 36, and 48. Treatment duration was 48 weeks, with an extension up through 144 weeks. The trial was conducted at 39 study centers in France, Germany, the United Kingdom, and the United States from 01/06/2009 to 01/15/2010.

The primary objective of Study 1100.1526 was to demonstrate the efficacy of nevirapine XR based regimen for HIV-1 infected patients who received nevirapine IR based regimen for at least 18 prior weeks of therapy. The primary endpoint was proportion of patients with sustained virologic response (SVR) through Week 24, using 50 copies/mL as the Lower Limit of Quantification (LLOQ 50 copies/mL) for HIV-1 RNA viral load. A virologic response was defined as two consecutive measurements of viral load <50 copies/mL which were at least 2 weeks apart. A virologic failure was defined by viral load  $\geq$ 50 copies/mL measured at two consecutive visits which were at least 2 weeks apart. A virologic rebound was defined as two consecutive measurements of a viral load  $\geq$  50 copies/mL, at least 2 weeks apart, following a virologic response. A patient was considered as a treatment failure at the earliest time of any one of the following events prior to Week 24:

- A virologic failure;
- A change of ARV therapy defined as either a permanent discontinuation of study medicine (nevirapine XR or nevirapine IR), addition of new ARV drugs, or alterations in background therapy that were not due to toxicity/intolerance attributable to the background therapy;
- Death;
- Lost to follow-up.

A change in the background therapy due to toxicity or intolerance clearly attributable to the background therapy was not considered as treatment failure. A sustained virologic response (SVR) had no virologic rebound or treatment failure through Week 24. The time window of Week 24 was  $24 \pm 4$  weeks from Day 1 defined as the day a patient started study treatment.

The secondary objective of Study 1100.1526 was to assess the safety and tolerance of nevirapine XR based regimen for HIV-1 infected patients who had received a stable nevirapine IR based regimen for at least 18 prior weeks of therapy. The secondary efficacy endpoints included:

- Proportion of sustained virologic response (viral load  $<50$  copies/mL) through Week 48. The time window of Week 48 was defined as  $48 \pm 4$  weeks from Day 1;
- Proportion of sustained virologic response (viral load  $<400$  copies/mL) through
  - Week 24;
  - Week 48;
- Time to loss of virologic response, defined as the time between the start of treatment and the time of treatment failure, up to and including the time when the last patient was on treatment for
  - 24 weeks;
  - 48 weeks;
- Change in and CD4+ cell count from baseline at each visit;
- Genotypic resistance associated with virologic failure.

### 3.2.2 Statistical Methodologies

Three analysis datasets were defined in the Study 1100.1526 protocol as follows:

- Treated Set (TS): This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
- Full Analysis Set (FAS): FAS is the same as TS.
- Per Protocol Set (PPS): This was a subset of the TS, excluding patients with important protocol violations in the TS.

The primary efficacy analysis was the test of non-inferiority of nevirapine XR to nevirapine IR with a non-inferiority margin  $\Delta = -12\%$  based on the FAS. A 95% confidence interval (CI) for the difference in the proportions of virologic response between nevirapine XR and nevirapine IR treatment groups was obtained using Cochran's statistic incorporating strata with continuity correction for the variance. Non-inferiority of nevirapine XR to nevirapine IR was established if the lower bound of the CI was greater than  $-12\%$ . A  $-10\%$  non-inferiority margin was later added

for secondary analysis according to a pre-NDA teleconference discussion (10/19/2009) with FDA and prior to the 24-week database lock.

Because of different methods used for assaying HIV-1 viral load (Amplicor-corrected, TaqMan-only) and different algorithms utilized for estimating virologic response (TLOVR, SNAPSHOT), each patient could have 4 viral load profiles: TLOVR method Amplicor-corrected profile, TLOVR method TaqMan-only profile, SNAPSHOT method Amplicor-corrected profile, SNAPSHOT method TaqMan-only profile. The primary efficacy endpoint was SVR using LLOQ  $\leq 50$  copies/mL based on the TLOVR algorithm and the Amplicor-corrected viral load assessment.

*Reviewer's comments: According to initial protocol, plasma samples for viral load determinations were obtained at every study visit and processed using the TaqMan assay. Because of a protocol amendment on 06/19/2009 which introduced the Amplicor assay method into the study, plasma samples with TaqMan results  $\geq 48$  and  $\leq 200$  copies/mL from Week 4 to Week 24 inclusive were also assayed using the Amplicor method. In addition, if the Amplicor assay detected virus ( $\geq 50$  copies/mL) in the tested sample, the samples obtained before and after the sample were also tested using the Amplicor assay. If no virus was detected by Amplicor on the initial TaqMan sample, no further Amplicor testing was performed. In this way, virologic failure was defined as detectable viral load ( $\geq 50$  copies/mL) on two consecutive plasma samples using the Amplicor assay.*

*Due to re-assay of some specimens using Amplicor test, some patients had both TaqMan test and Amplicor test results available at some specified visits. Two viral load profiles were constructed for each patient. The first one was solely based on TaqMan test (TaqMan-only profile). The second one used TaqMan test as the base, but used Amplicor test results to replace TaqMan test results whenever possible (Amplicor-corrected profile).*

Analyses of the secondary endpoints, proportion of sustained virologic response (viral load  $< 50$  copies/mL) through Week 48 or proportion of sustained virologic response (viral load  $< 400$  copies/mL) were similar to the primary endpoint. Time to loss of virologic response was analyzed using the Cox proportional hazard model, with baseline background therapy as a covariate. HIV-1 viral load and CD4+ cell counts were analyzed descriptively.

Methods for handling of missing data were pre-specified in the protocol. For efficacy endpoints related to SVR through Week 24, the non-completers considered failure approach was used for patients that discontinued the study. All planned visits that were missing were considered virologic failures unless the patient was a responder at the preceding and following visits. For analyses of change from baseline, missing viral load and CD4+ cell count data was replaced by the last observation in the last observation carried forward (LOCF) analysis.

The trial was initially planned to enroll 300 patients, 200 in the nevirapine XR group and 100 in the nevirapine IR group, respectively. The sample size calculation assumed a 90% virologic response rate, a one-sided  $\alpha = 0.025$ , and a randomization ratio of 2:1 in the two treatment arms. As such, 198 and 99 patients respectively were needed in order to have 90% power to reject the

hypothesis that the neviapine XR formulation was inferior to nevirapine IR formulation with a margin  $\geq 12\%$  in terms of the proportion with sustained virologic response.

*Reviewer's comments: The trial enrolled and randomized 445 patients which were 145 (48.3%) more than originally planned. Please see Section 3.2.5 for additional analysis based on data from the first 300 or so patients.*

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 445 subjects were enrolled and randomized, all but two received at least one dose of study treatment. Of the 443 treated subjects, 432 (97.5%) completed 24 weeks of study treatment. The completeness of follow-up was similar in the nevirapine IR group (97.3%) and the nevirapine XR group (97.6%). There were 11 patients who discontinued the trial before Week 24, 3 (Patient 3405, Patient 4038, and Patient 4163 in NVP XR) due to adverse events, 2 (Patient 1518 in NVP IR and Patient 4020 in NVP XR) due to loss to follow up, 1 (Patient 2500 in NVP IR) due to consent withdrawal, 2 (Patient 1007 and Patient 2542 in NVP XR) due to non compliance, 1 (Patient 1524 in NVP IR) due to lack of efficacy, 1 (Patient 2501 in NVP XR) due to pregnancy, and 1 (Patient 1654 in NVP IR) due to other reasons. The Treated Set (TS) included 443 patients who took at least one dose of trial medication, which was the same as the Full Analysis Set (FAS). The Per Protocol Set (PPS) contained 440 patients, excluding 3 patients (Patient 1095 in the NVP IR group, Patient 1080 and Patient 2048 in the NVP XR group) with important protocol violations. Table 1 below shows number of subjects discontinued prematurely and numbers included in different analyses.

**Table 1 Patients Disposition up to Week 24**

	NVP IR 200 BID	NVP XR 400 QD	Total
<b>Enrolled</b>			499
<b>Randomized</b>	149	296	445
<b>Treated (N[%])*</b>	148 (100.0)	295 (100.0)	443 (100.0)
<b>Completed Week 24 visit** (N[%])</b>	144 (97.3)	288 (97.6)	432 (97.5)
<b>Prematurely discontinued before Week 24 visit (N[%])</b>	4 (2.7)	7 (2.4)	11 (2.5)
Adverse events	0	3	3
Loss to follow-up	1	1	2
Consent withdrawn	1	0	1
Non compliance	0	2	2
Lack of efficacy	1	0	1
Pregnancy	0	1	1
Other	1	0	1
<b>Number of Patients in Efficacy Analyses</b>			
Treated Set (TS)	148	295	443
Full Analysis Set (FAS)	148	295	443
Per Protocol Set (PPS)***	147	293	440

\*Two patients (Patients 2548 and 4627) were randomized but not treated

\*\* Include 2 patients (Patients 1367 and 4653 in the XR group) whose Week 24 visits was completed but was outside of the 24 +/- 4 weeks window and 1 patient in the IR group who missed Week 24 visit but was still on study.

\*\*\*Three patients (1 in the IR group and 2 in the XR group) with an important protocol violation were excluded. Patient 1095 in the IR group and Patient 1080 in XR group had received less than 18 weeks of nevirapine IR prior to randomization. Patient 2048 in the XR group had a detectable viral load in the four months prior to screening.

Selected demographic characteristics were compared between treatment groups in Table 2. The majority of patients were male: 86.5% in the nevirapine IR and 82.7% in the nevirapine XR groups, respectively. The mean age of the patients was 47.4 years and 55.8% of the patients were between 41 and 55 years of age. The majority of patients in both treatment groups were white (91.2%), non Hispanic/Latino (90.5%), and over 66% of patients in each group were from Europe. The proportions of major demographic subgroups were similar between the treatment groups.

**Table 2 Demographic Data – FAS**

		<b>NVP IR 200 BID N=148</b>	<b>NVP XR 400 QD N=295</b>	<b>Total N=443</b>
<b>Age[years]</b>	N	148	295	443
	Mean	47.6	47.3	47.4
	SD	9.8	9.6	9.7
<b>Age group [N (%)]</b>	18-40	36 ( 24.3)	70 ( 23.7)	106 ( 23.9)
	41-55	79 ( 53.4)	168 ( 56.9)	247 ( 55.8)
	> 55	33 (22.3)	57 (19.3)	90 (20.3)
<b>Gender [N (%)]</b>	Male	128 ( 86.5)	244 ( 82.7)	372 ( 84.0)
	Female	20 ( 13.5)	51 ( 17.3)	71 ( 16.0)
<b>Race [N (%)]</b>	White	134 ( 90.5)	270 ( 91.5)	404 ( 91.2)
	Black	13 ( 8.8)	20 ( 6.8)	33 ( 7.4)
	Asian	0 ( 0.0)	5 ( 1.7)	5 ( 1.1)
	Hawaiian/Pacific Islander	1 ( 0.7)	0 ( 0.0)	1 ( 0.2)
<b>Hispanic/Latino [N (%)]</b>	Yes	16 ( 10.8)	26 ( 8.8)	42 ( 9.5)
	No	132 ( 89.2)	269 ( 91.2)	401 ( 90.5)
<b>Region [N (%)]</b>	North America	46 ( 31.1)	98 ( 33.2)	144 ( 32.5)
	Europe	102 ( 68.9)	197 ( 66.8)	299 ( 67.5)

Table 3 summarizes key baseline characteristics. In the nevirapine IR group vs. nevirapine XR group, Truvada<sup>®</sup> was the background in 55.4% and 53.6%, respectively; Combivir<sup>®</sup> in 20.3% and 21.4%, respectively; and Kivexa<sup>®</sup>/Epzicom<sup>®</sup> in 24.3% and 25.1%, respectively. Due to stratification, the proportions of patients receiving different backgrounds were similar in the two treatment groups with most patients having received Truvada<sup>®</sup>. Most of the patients (91.9% for nevirapine IR and 94.9% nevirapine XR) had baseline HIV-1 RNA counts <50 copies/mL. There were 27 patients (6.1%) with baseline HIV-1 viral loads ≥50 copies/mL included in the study due to non-detectable screening results. The majority of patients had baseline CD4+ cell counts ≥400 cells/mm<sup>3</sup>: 78.4% in the nevirapine IR group and 75.6% in the nevirapine XR group. The majority of patients had no history of AIDS-defining illness, 79.7% of patients in the nevirapine IR group and 74.9% in the nevirapine XR group. According to the CDC class, 65.5% of patients in the nevirapine IR group and 59.0% of patients in the nevirapine XR group were classified as non-AIDS (A1, A2, B1, and B2). The modes of transmission included male having sex with

male (72.5%) and partner infected (44.5%). These baseline characteristics are comparable between the two treatment groups.

*Reviewer's comments: Additional analysis was performed in Section 3.2.5 excluding these 27 patients with baseline HIV-1 viral loads  $\geq 50$  copies/mL.*

**Table 3 Baseline characteristics – FAS**

	<b>NVP IR 200 BID N=148</b>	<b>NVP XR 400 QD N=295</b>	<b>Total N=443</b>
<b>Background therapy [N (%)]</b>			
Truvada	82 ( 55.4)	158 ( 53.6)	240 ( 54.2)
Combivir	30 ( 20.3)	63 ( 21.4)	93 ( 21.0)
Kivexa/Epzicom	36 ( 24.3)	74 ( 25.1)	110 ( 24.8)
<b>Baseline CD4+ count (cells/mm<sup>3</sup>) *(N [%])</b>			
>50 - 200	2 ( 1.4)	6 ( 2.0)	8 ( 1.8)
>200 - 350	17 ( 11.5)	43 ( 14.6)	60 ( 13.5)
>350 - <400	12 ( 8.1)	23 ( 7.8)	35 ( 7.9)
$\geq 400$	116 ( 78.4)	223 ( 75.6)	339 ( 76.5)
Missing	1 ( 0.7)	0 ( 0.0)	1 ( 0.2)
<b>CDC class (N [%])</b>			
Non-AIDS (A1, A2, B1, B2)	97 ( 65.5)	174 ( 59.0)	271 ( 61.2)
AIDS (A3, B3)	26 ( 17.6)	65 ( 22.0)	91 ( 20.5)
AIDS (C1, C2, C3)	25 ( 16.9)	56 ( 19.0)	81 ( 18.3)
<b>Baseline HIV-1 RNA (copies/mL)* (N [%])</b>			
<50	136 ( 91.9)	280 ( 94.9)	416 ( 93.9)
$\geq 50$	12 ( 8.1)	15 ( 5.1)	27 ( 6.1)
<b>History of AIDS-defining illness (N [%])</b>			
Yes	118 ( 79.7)	221 ( 74.9)	339 ( 76.5)
No	30 ( 20.3)	74 ( 25.1)	104 ( 23.5)
<b>Mode of transmission ** (N [%])</b>			
N	142 ( 95.9)	285 ( 96.6)	427 ( 96.4)
Male had sex with male	108 ( 73.0)	213 ( 72.2)	321 ( 72.5)
Partner infected	62 ( 41.9)	135 ( 45.8)	197 ( 44.5)
Injection drug user	4 ( 2.7)	9 ( 3.1)	13 ( 2.9)
Transfusion	4 ( 2.7)	9 ( 3.1)	13 ( 2.9)
Occupational exposure	1 ( 0.7)	3 ( 1.0)	4 ( 0.9)
Other	2 ( 1.4)	17 ( 5.8)	19 ( 4.3)

\* Baseline values are calculated as the average of the last two measurements prior to the start of randomized treatment. HIV-1 RNA viral load is based on TaqMan assay results.

\*\* A patient may have multiple modes of transmission.

### 3.2.4 Efficacy Results

#### Primary Efficacy Endpoint

The primary efficacy assessment was based on the non-inferiority analyses of proportion of patients with sustained virologic response (SVR) through Week 24. Patients who discontinued the study early (11 patients), or for who had viral load missing at Week 24 (3 patients), or whose Week 24 visit were out of the 24 ± 4 weeks window (2 patients) were considered to be failures. Additionally, some patients (15 per Amplicor-corrected assay and 28 per TaqMan-only assay) who responded earlier and then rebounded were also considered as virologic failures.

Table 4 presents study outcome through Week 24 using TLOVR algorithm and FAS dataset. Based on Amplicor-corrected assay, 92.6% of the patients in the nevirapine IR treatment group were responders through Week 24 whereas 93.6% of the patients in the nevirapine XR group were responders through Week 24. Using TaqMan-only assay, the proportion of patients with sustained virologic response was 89.9% in nevirapine IR group and 91.2% in the nevirapine XR group, respectively. The TaqMan assay seemed to identify slightly more patients with detectable HIV-1 viral loads than the Amplicor assay.

**Table 4 Study Outcome through Week 24 with LLOQ 50 copies/mL - TLOVR - FAS**

	Amplicor-corrected		TaqMan-only	
	NVP IR 200 BID N=148	NVP XR 400 QD N=295	NVP IR 200 BID N=148	NVP XR 400 QD N=295
<b>Responder</b>	137 (92.6%)	276 (93.6%)	133(89.9%)	269 (91.2%)
<b>Failure</b>	11 (7.4%)	19 (6.4%)	15 (10.1%)	26 (8.8%)
<i>Virologic failure</i>	8 (5.4%)	12 (4.1%)	13 (8.8%)	19 (6.4%)
Rebound	5	10	11	17
Other	3**	2‡	2*	2‡
<b>Discontinued study drug before Week 24</b>	3 (2.0%) <sup>†</sup>	7 (2.4%)	2 (1.3%) <sup>†</sup>	7 (2.4%)

<sup>†</sup> One patient in the IR group (Patient 1524) discontinued due to lack of efficacy but classified as rebounder.

<sup>‡</sup> Two patients in the XR group (Patients 1367 and 4653) had Week 24 visit out of the 24 ± 4 weeks window.

\* Two patients (Patients 1157 and 2545) had Week 24 visit viral load missing

\*\* For the 3 patients in the IR group, two (Patients 1157 and 2545) had Week 24 visit viral load missing and one (Patient 2144) missed Week 24 visit but was still on study. Patient 2144 was classified as a rebound using TaqMan-only method.

Table 5 summarizes analyses of the primary efficacy endpoint using combinations of different analysis datasets, methods and assays. The protocol specified primary analysis (shaded row) was sustained HIV-1 viral load suppression using TLOVR algorithm, Amplicor-corrected assay, and based on FAS. A sustained virologic response was observed in 92.6% of nevirapine IR patients and 93.6% of nevirapine XR patients. Adjusting for background therapy, the difference was 1.0% in favor of nevirapine XR with 95% CI (-4.3%, 6.2%). The lower bound of the difference was above -12% (pre-specified non-inferiority margin) and also above -10% (additional non-inferiority margin added prior to database lock); thus, demonstrating the non-inferiority of nevirapine XR to nevirapine IR treatment. Similarly, based on the SNAPSHOT approach and the Amplicor-corrected assay, 93.9% of patients in the nevirapine IR treatment group and 95.3% of patients in the nevirapine XR group were responders at the Week 24. The difference was 1.3% favoring nevirapine XR with 95% CI (-3.5%, 6.1%). In all cases, the proportion of patients with sustained virologic response was at least 90% in both groups. Patients who transitioned from nevirapine IR to nevirapine XR regimen had about 1% to 2% higher response rate than those who continued on nevirapine IR therapy. The non-inferiority of nevirapine to nevirapine IR was established as all lower bounds of the 95% CI were above the -12% non-inferiority margin (also above -10% additional non-inferiority margin).

**Table 5 Analysis of Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL (No. with response/Total No. [%])**

Analysis Dataset	Method	Assay	NVP IR 200 BID	NVP XR 400 QD	Difference (XR – IR) in % (95% CI)
FAS	TLOVR	Amplicor-corrected	137/148 (92.6)	276/295 (93.6)	1.0 (-4.3, 6.2)
FAS	TLOVR	TaqMan-only	133/148 (89.9)	269/295 (91.2)	1.3 (-4.7, 7.3)
FAS	SNAPSHOT	Amplicor-corrected	139/148 (93.9)	281/295 (95.3)	1.3 (-3.5, 6.1)
FAS	SNAPSHOT	TaqMan-only	137/148 (92.6)	279/295 (94.6)	2.0 (-3.2, 7.1)
PPS	TLOVR	Amplicor-corrected	136/147(92.5)	274/293(93.5)	1.0 (-4.3, 6.3)

## Secondary Efficacy Endpoints

The secondary endpoints included the proportion of patients with sustained virologic response through Week 24 using LLOQ 400 copies/mL, time to loss of virologic response, and change in viral load and CD4+ cell counts from baseline at each visit.

The TaqMan-only profile was used to calculate the response rate regarding LLOQ 400 copies/mL using the FAS. Based on the TLOVR algorithm, 94.6% of the patients in the nevirapine IR treatment group and 96.6% of the patients in the nevirapine XR group were responders through Week 24. The difference was 2.0% and the lower bound of the 95% CI for the difference in the proportion was 2.5%. Same results were obtained based on the SNAPSHOT method.

The Cox proportional hazard model was used for analyzing time to loss of virologic response with adjustment for background therapy. No significant difference in time to loss of virologic response was detected between the two treatment groups. For Amplicor-corrected profile, the hazard ratio of nevirapine XR versus IR was 0.88 with 95% CI (0.42, 1.86). For TaqMan-only profile, the hazard ratio was 0.89 with 95% CI (0.47, 1.68). The Kaplan-Meier curves for both treatment groups were close to each other from baseline to Week 24 for both Amplicor corrected and TaqMan-only profiles.

Table 6 shows changes of HIV-1 viral load from baseline using observed values and measured with TaqMan-only assay. There was no significant difference between the two treatment groups. A single patient (Patient 4015 on nevirapine IR) rebounded from non-detectable at the baseline to a very high level (12,953 copies/mL) at Week 24 because of reduction in compliance. As patients entered the trial with viral load below detection, the clinical meaningfulness of measuring change from baseline is unclear.

**Table 6 Summary of HIV-1 viral load (copies/mL) and Change from Baseline by Visit - FAS - TaqMan**

Visit	NVP IR 200 BID			NVP XR 400 QD		
	N	Mean (SD)	Median	N	Mean (SD)	Median
Baseline	148	49.2 (11.2)	47.0	295	52.9 (64.4)	47.0
Week 2	146	50.4 (17.2)	47.0	292	48.8 (9.6)	47.0
Week 4	146	50.0 (14.8)	47.0	289	51.2 (25.1)	47.0
Week 8	144	54.9 (32.3)	47.0	285	49.7 (14.1)	47.0
Week 12	143	52.9 (29.4)	47.0	286	54.8 (72.4)	47.0
Week 24	141	140.3 (1091)	47.0	286	51.9 (54.1)	47.0
<b>Change from Baseline</b>						
Week 2	146	1.1 (20.4)	0.0	292	-4.2 (65.4)	0.0
Week 4	146	0.8 (18.8)	0.0	289	2.1 (30.4)	0.0
Week 8	144	5.6 (32.7)	0.0	285	-3.4 (65.2)	0.0
Week 12	143	3.6 (31.3)	0.0	286	1.9 (95.8)	0.0
Week 24	141	91.0 (1091)	0.0	286	-1.1 (84.1)	0.0

Table 7 presents changes in CD4+ cell counts from baseline using observed values. Both treatment groups demonstrated a trend of increasing mean CD4+ cell counts after Week 8, and there was no difference between the two treatment groups.

**Table 7 Summary of CD4+ Count (cells/mm<sup>3</sup>) and Change from Baseline by Visit - FAS**

Visit	NVP IR 200 BID			NVP XR 400 QD		
	N	Mean (SD)	Median	N	Mean (SD)	Median
Baseline	147	569.7 (215.6)	542.0	295	557.7 (213.2)	530.0
Week 2	141	574.7 (244.1)	532.0	280	552.7 (230.5)	517.0
Week 4	137	567.0 (209.8)	550.0	271	540.9 (222.8)	510.0
Week 8	139	550.3 (226.6)	508.0	281	532.7 (224.7)	501.0
Week 12	139	590.5 (288.5)	542.0	283	551.0 (227.9)	522.0
Week 24	143	622.7 (278.1)	585.0	282	609.0 (247.7)	558.0
<b>Change from Baseline</b>						
Week 2	141	3.7 (115.2)	-2.5	280	-4.7 (107.7)	-8.8
Week 4	137	0.8 (110.8)	6.0	271	-15.4 (114.1)	-15.0
Week 8	139	-18.6 (122.9)	-1.0	281	-24.4 (117.6)	-27.0
Week 12	139	22.3 (152.9)	6.5	283	-10.2 (118.5)	-7.5
Week 24	143	50.4 (162.8)	32.5	282	45.2 (137.6)	39.8

### 3.2.5 Additional Analyses

#### Analysis excluding 27 patients with baseline HIV-1 viral loads $\geq 50$ copies/mL

As described in Section 3.2.3, baseline HIV-1 viral load was calculated as the average of the screening Visit 1 value and the randomization Visit 2 value obtained approximately 3 weeks later. The study included 27 patients (12 in nevirapine IR group and 15 in nevirapine XR group) with detectable HIV-1 viral loads at randomization because of their screening results. Of the 12 patients in the nevirapine IR group, one (Patient 1358) had HIV-1 viral load of 160 copies/mL and the other 11 patients had values between 50 to 100 copies/mL at baseline. For the nevirapine XR group, the baseline HIV-1 viral load was 1103 copies/mL for 1 patient (1515), 358 copies/mL for 1 patient (1001),  $\geq 100$  copies/mL for 3 patients (1355, 1509, 4502), and  $< 100$  copies/mL for the other 10 patients. Analysis was performed on the 416 patients excluding 27 with HIV-viral load  $\geq 50$  copies/mL. Based on TLOVR algorithm and Amplicor-corrected assay, 127/136 (93.4%) of the patients treated with nevirapine IR and 264/280 (94.3%) of the patients treated with nevirapine XR had sustained virologic response through Week 24. The response rate based on TLOVR algorithm and TaqMan-only assay was 126/136 (92.6%) for the nevirapine IR group and 261/280 (93.2%) for the nevirapine XR group, respectively. Analysis of the primary efficacy endpoints excluding these 27 patients generated similar results as those from the primary efficacy analysis.

#### Analysis of the first 300 or so patients

The protocol planned sample size was 300 patients, 200 in the nevirapine XR group and 100 in the nevirapine IR group, respectively. The trial enrolled and randomized 445 patients; all but two received at least one dose of study treatment. All patients were randomized between 01/15/2009 and 02/18/2009. The protocol specified enrollment goal was reached within 3 weeks, with 302

patients randomized on or before 02/04/2009. In order to assess the impact of over enrollment, an analysis of sustained virologic response was performed for these first 302 patients which included 101 in the nevirapine IR group and 201 in the nevirapine XR group. Based on TLOVR algorithm and Amplicor-corrected assay, 92/101 (91.1%) of the patients treated with nevirapine IR and 192/201 (95.5%) of the patients treated with nevirapine XR had sustained virologic response through Week 24. The response rate based on TLOVR algorithm and TaqMan-only assay was 88/101 (87.1%) for the nevirapine IR group and 188/201 (93.5%) for the nevirapine XR group, respectively. Analysis of the primary efficacy endpoints using the first 302 patients generated consistent findings as those from the primary efficacy analysis.

### Discordance analysis

As described in Section 3.2.2, both TaqMan and Amplicor-corrected methods were used for assaying HIV-1 viral load. A comparison of these two assays in defining sustained virologic response is presented in Table 9. The discordance rate was 4.74% with TLOVR algorithm and 1.36% with SNAPSHOT algorithm. For instance, under TLOVR algorithm, 16 out of 443 patients (3.61%) were classified as responders by Amplicor-corrected assay but as non-responders by TaqMan assay while 5 patients (1.13%) were classified as non-responders by Amplicor-corrected assay but as responders by TaqMan assay. The associated Cohen's kappa coefficient is 0.6791 for the TLOVR method and 0.8729 for the SNAPSHOT method. While there are no universal criteria for the rating of Kappa statistics, based on Fleiss's equally arbitrary guidelines, a Kappa value over 0.75 are characterized as excellent, 0.40 to 0.75 as fair to good, and below 0.40 as poor. Hence, the agreement between TaqMan and Amplicor-corrected assays in processing plasma samples and defining sustained virologic response may be considered excellent for both TLOVR and SNAPSHOT algorithm.

**Table 8 Comparison of TaqMan assay and Amplicor-corrected Assay in Defining Sustained Virologic Response at Week 24**

Response with LLOQ 50 copies/mL		TLOVR		SNAPSHOT	
Amplicor-corrected	TaqMan	N	%	N	%
Yes	Yes	397	89.62	415	93.68
No	No	25	5.64	22	4.97
Yes	No	16	3.61	5	1.13
No	Yes	5	1.13	1	0.23
<b>Total</b>		443	100.00	443	100.00
<b>Kappa</b>		0.6791		0.8729	
<b>P-value</b>		<.0001		<.0001	

### 3.3 Evaluation of Safety

During the 24 weeks of study treatment, there was a higher frequency of patients in the nevirapine XR group than the nevirapine IR group with any adverse events (75.6% vs. 60.1%). However, the rate of patients with adverse events of DAIDS Grade severity 3 or 4 was similar in the nevirapine XR and nevirapine IR groups (3.7% and 4.1%, respectively). The percentage of investigator-defined drug related adverse events was 11.9% in the nevirapine XR group vs. 2.0% in the nevirapine IR group.

A total of 21 patients had serious adverse events with 17 in the nevirapine XR group (5.8%) and 4 in the nevirapine IR group (2.7%). None of these events were considered causally related to the drug. There were no life-threatening or fatal events. There were 3 adverse events which led to study discontinuation, all of which were in the nevirapine XR group.

While there were a higher number of adverse events in the nevirapine XR group, the interpretation of this higher rate is difficult in the setting of an open, randomized trial in which both patients and investigators were aware of the treatment assignment.

*Reviewer's comments: The above is just a summary of the safety results presented by the sponsor in the study reports. For details, please see the medical officer's review.*

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In Study 1100.1526, analyses of subpopulations revealed no relationship between the proportion of sustained virologic response through Week 24 and any baseline demographic (age group, gender, race, ethnicity and region) or clinical characteristic, including type of background therapy received, nevirapine as the first HAART regimen, and duration of previous nevirapine IR treatment.

### 4.1 Gender, Race, Age, and Geographic Region

Study 1100.1526 was conducted in 39 centers in a wide geographic region including Europe and North America. The proportion of patients with sustained virologic response through Week 24 with LLOQ 50 copies/mL was investigated with respect to age, gender, race, ethnicity, and region (Table 9 for Amplicor-corrected Assay and Table 10 for TaqMan assay). Differences in sustained virologic responses are presented for subgroups with at least 20 subjects in each treatment arm. For subgroups with relatively large numbers of patients, the nevirapine XR treatment group tended to have slightly higher proportions of patients with continued viral load suppression than the nevirapine IR group. Overall, there was no relationship between the proportion of virologic responders at Week 24 and age group, gender, race, ethnicity, and region for either treatment group. This is consistent with the results in the overall study population. Note analysis under SNAPSHOT algorithm was performed by this reviewer.

**Table 9 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Demographics (No. with response/Total No.[%]) – FAS - Amplacor-corrected**

	TLOVR			SNAPSHOT		
	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)
<b>Age (years)</b>						
18-40	30/ 36 (83.3)	64/ 70 (91.4)	8.1	31/36 (86.1)	66/70 (94.3)	8.2
41-55	75/ 79 (94.9)	160/168 (95.2)	0.3	76/79 (96.2)	162/168 (96.4)	0.2
> 55	32/ 33 (97.0)	52/ 57 (91.2)	-5.8	32/33 (97.0)	53/57 (93.0)	-4.0
<b>Gender</b>						
Male	119/128 (93.0)	229/244 (93.9)	0.9	121/128 (94.5)	234/244 (95.9)	1.4
Female	18/ 20 (90.0)	47/ 51 (92.2)	2.2	18/20 (90.0)	47/51 (92.2)	2.2
<b>Race</b>						
White	124/134 (92.5)	254/270 (94.1)	1.6	126/134 (94.0)	259/270 (95.9)	1.9
Black	12/ 13 (92.3)	18/ 20 (90.0)		12/13 (92.3)	18/20 (90.0)	
Asian	0/ 0 (0)	4/ 5 (80.0)		0/0 (0)	4/5 (80.0)	
Hawaiian/Pacific Islander	1/ 1 ( 100)	0/ 0 (0)		1/1 (100)	0/0 (0)	
<b>Hispanic/Latino</b>						
Yes	15/ 16 (93.8)	25/ 26 (96.2)		16/16 (100)	25/26 (96.2)	
No	122/132 (92.4)	251/269 (93.3)	0.9	123/132 (93.2)	256/269 (95.2)	2.0
<b>Region</b>						
North America	43/ 46 (93.5)	91/ 98 (92.9)	-0.6	44/46 (95.7)	91/98 (92.9)	-2.8
Europe	94/102 (92.2)	185/197 (93.9)	1.7	95/102 (93.1)	190/197 (96.4)	3.3

**Table 10 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Demographics (No. with response/Total No.[%]) – FAS - TaqMan**

	TLOVR			SNAPSHOT		
	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)
<b>Age (years)</b>						
18-40	27/ 36 (75.0)	64/ 70 (91.4)	16.4	29/36 (80.6)	65/70 (92.9)	12.3
41-55	75/ 79 (94.9)	151/168 (89.9)	-5.0	76/79 (96.2)	160/168 (95.2)	-1.0
> 55	31/ 33 (93.9)	54/ 57 (94.7)	0.8	32/33 (97.0)	54/57 (94.7)	-2.3
<b>Gender</b>						
Male	115/128 (89.8)	222/244 (91.0)	1.2	119/128 (93.0)	231/244 (94.7)	1.7
Female	18/ 20 (90.0)	47/ 51 (92.2)	2.2	18/20 (90.0)	48/51 (94.1)	4.1
<b>Race</b>						
White	120/134 (89.6)	247/270 (91.5)	1.9	124/134 (92.5)	257/270 (95.2)	2.7
Black	12/ 13 (92.3)	18/ 20 (90.0)		12/13 (92.3)	18/20 (90.0)	
Asian	0/ 0 (0)	4/ 5 (80.0)		0/0 (0)	4/5 (80.0)	
Hawaiian/Pacific Islander	1/ 1 ( 100)	0/ 0 (0)		1/1 (100)	0/0 (0)	
<b>Hispanic/Latino</b>						
Yes	16/ 16 ( 100)	25/ 26 (96.2)	-3.8	16/16 (100)	25/26 (96.2)	-3.8
No	117/132 (88.6)	244/269 (90.7)	2.1	121/132 (91.7)	254/269 (94.4)	2.7
<b>Region</b>						
North America	44/ 46 (95.7)	89/ 98 (90.8)	-4.9	44/46 (95.7)	90/98 (91.8)	-3.9
Europe	89/102 (87.3)	180/197 (91.4)	4.1	93/102 (91.2)	189/197 (95.9)	4.7

## 4.2 Other Special/Subgroup Populations

Study 1100.1526 employed stratified randomization method in patient allocation, where eligible patients for the trial were stratified based on three background medications: Truvada®, Combivir®, or Kivexa®/Epzicom™. The effect of background ARV therapy on sustained Virologic Response was examined in Table 11. Based on the TLOVR algorithm and Amplicor-corrected assay, patients in the nevirapine IR group who received Epzicom/Kivexa as background therapy had a lower response rate (86.1%) than any other nevirapine IR or nevirapine XR background ARV subgroups. Out of the 5 nevirapine IR failures, 3 were for missing observations and 2 had rebound. There was a difference in response rate of 11.2% favoring nevirapine XR treatment in the Epzicom/Kivexa subgroup according to the TLOVR method and Amplicor-corrected assay. Those in the Truvada and Combivir groups showed smaller differences of 2.1% and -3.0%, respectively, favoring nevirapine IR treatment. For patients receiving Combivir, the sustained virologic response rate appeared to be higher in the IR group than the XR group according to the TLOVR method. While the proportion of patients with continued suppression varied by background therapy, no important pattern was observed between the background ARV and nevirapine treatment.

**Table 11 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by background ARV therapy (No. with response/Total No.[%]) - FAS**

Method	Assay	background ARV therapy	NVP IR 200 BID N=148	NVP XR 400 QD N=295	Difference (XR – IR) in % (95% CI)
TLOVR	Amplicor-corrected	Truvada	77/82 (93.9)	145/158 (91.8)	-2.1 (-8.9, 4.6)
		Combivir	29/30 (96.7)	59/63 (93.7)	-3.0 (-11.8, 5.8)
		Kivexa/Epzicom	31/36 (86.1)	72/74 (97.3)	11.2 (-0.7, 23.1)
TLOVR	TaqMan-only	Truvada	73/82 (89.0)	144/158 (91.1)	2.1 (-6.0, 10.2)
		Combivir	28/30 (93.3)	57/63 (90.5)	-2.9 (-14.4, 8.6)
		Kivexa/Epzicom	32/36 (88.9)	68/74 (91.9)	3.0 (-9.0, 15.0)
SNAPSHOT	Amplicor-corrected	Truvada	77/82 (93.9)	148/158 (93.7)	-0.2 (-6.7, 6.2)
		Combivir	29/30 (96.7)	61/63 (96.8)	0.2 (-7.6, 7.9)
		Kivexa/Epzicom	33/36 (91.7)	72/74 (97.3)	5.6 (-4.1, 15.4)
SNAPSHOT	TaqMan-only	Truvada	75/82 (91.5)	148/158 (93.7)	2.2 (-4.9, 9.3)
		Combivir	29/30 (96.7)	60/63 (95.2)	-1.4 (-9.7, 6.9)
		Kivexa/Epzicom	33/36 (91.7)	71/74 (95.9)	4.3 (-5.8, 14.4)

Tables 12 and 13 present analysis of the primary efficacy endpoint by additional baseline characteristics, including CD4+ cell count, CDC class, HIV-1 baseline viral load, nevirapine as first Highly Active Antiretroviral Therapy (HAART) regimen, duration of previous nevirapine IR treatment, and type of previous background therapy prior to study medication. Differences in sustained virologic responses are presented for subgroups with at least 20 subjects in each treatment arm. There appears to be higher sustained virologic response associated with nevirapine XR treatment, with the most difference observed in the CDC class AIDS (A3 B3) subgroup. In general, no important patterns for response were observed for patients for each subgroup. Note analysis under SNAPSHOT algorithm was performed by this reviewer.

**Table 12 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Characteristics (No. with response/Total No.[%]) – FAS -Amplicor-corrected**

	TLOVR			SNAPSHOT		
	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)
<b>Baseline CD4+ count (cells/mm<sup>3</sup>)</b>						
>50 - 200	2/ 2 ( 100)	6/ 6 ( 100)		2/ 2 ( 100)	6/ 6 ( 100)	
>200 - 350	11/ 17 (64.7)	40/ 43 (93.0)		13/17 (76.5)	41/43 (95.3)	
>350 - <400	11/ 12 (91.7)	21/ 23 (91.3)		11/12 (91.7)	21/23 (91.3)	
>= 400	112/116 (96.6)	209/223 (93.7)	-2.9	112/116 (96.6)	213/223 (95.5)	-1.1
Missing	1/ 1 ( 100)	0/ 0 ( 0)		1/1 (100)	0/0 (0)	
<b>CDC class</b>						
Non-AIDS (A1, A2, B1, B2)	93/ 97 (95.9)	163/174 (93.7)	-2.2	94/97 (96.9)	166/174 (95.4)	-1.5
AIDS (A3 B3)	20/ 26 (76.9)	60/ 65 (92.3)	15.4	21/26 (80.0)	61/65 (93.8)	13.8
AIDS (C1, C2, C3)	24/ 25 (96.0)	53/ 56 (94.6)	-1.4	24/25 (96.0)	54/56 (96.4)	0.4
<b>Baseline HIV-1 RNA (copies/mL)</b>						
<50	127/136 (93.4)	264/280 (94.3)	0.9	129/136 (94.9)	269/280 (96.1)	1.2
>= 50	10/ 12 (83.3)	12/ 15 (80.0)		10/12 (83.3)	12/ 15 (80.0)	
<b>NVP as the first HAART regimen</b>						
Yes	67/ 73 (91.8)	125/134 (93.3)	1.5	68/73 (93.2)	128/134 (95.5)	2.2
No	70/ 75 (93.3)	151/161 (93.8)	0.5	71/75 (94.7)	153/161 (95.0)	0.3
<b>Duration of previous NVP IR treatment</b>						
<1 year	27/ 30 (90.0)	49/ 52 (94.2)	4.2	28/30 (93.3)	49/52 (94.2)	0.9
1-3 years	38/ 44 (86.4)	94/101 (93.1)	6.7	39/44 (88.6)	97/101 (96.0)	7.4
3-5 years	34/ 35 (97.1)	70/ 75 (93.3)	-3.8	34/35 (97.1)	70/75 (93.3)	-3.8
>5 years	38/ 39 (97.4)	63/ 67 (94.0)	-3.4	38/39 (97.4)	65/67 (97.0)	-0.4
<b>Type of background regimen prior to NVP</b>						
PI based	26/ 28 (92.9)	57/ 58 (98.3)	5.4	26/28 (92.9)	57/58 (98.3)	5.4
NNRTI based	8/ 8 ( 100)	21/ 23 (91.3)		8/8 (100)	21/23 (91.3)	
PI based and NNRTI based	11/ 11 ( 100)	23/ 27 (85.2)		11/11 (100)	25/27 (92.6)	
NRTI*	25/ 28 (89.3)	50/ 53 (94.3)	5.0	26/28 (92.9)	50/53 (94.3)	1.4

\* Previous regimens were NRTI only (ABC, 3TC, and ZDV) or included ABC, 3TC, and ZDV as part of the background

**Table 13 Sustained Virologic Response at Week 24 with LLOQ 50 copies/mL by Baseline Characteristics (No. with response/Total No.[%]) – FAS - TaqMan**

	TLOVR			SNAPSHOT		
	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)	NVP IR 200 BID N=148	NVP XR 400 QD N=295	(XR – IR) (%)
<b>Baseline CD4+ count (cells/mm<sup>3</sup>)</b>						
>50 - 200	1/ 2 (50.0)	5/ 6 (83.3)		1/ 2 (50.0)	6/6 (100)	
>200 - 350	13/ 17 (76.5)	39/ 43 (90.7)		13/17 (76.5)	40/43 (93.0)	
>350 - <400	10/ 12 (83.3)	20/ 23 (87.0)		10/12 (83.3)	21/23 (91.3)	
>= 400	108/116 (93.1)	205/223 (91.9)	-1.2	112/116 (96.6)	212/223 (95.1)	-1.5
Missing	1/ 1 ( 100)	0/ 0 ( 0)		1/1 (100)	0/0 (0)	
<b>CDC class</b>						
Non-AIDS (A1, A2, B1, B2)	91/ 97 (93.8)	159/174 (91.4)	-2.4	93/97 (95.9)	165/174 (94.8)	-1.1
AIDS (A3 B3)	20/ 26 (76.9)	58/ 65 (89.2)	12.3	20/26 (76.9)	61/65 (93.8)	16.9
AIDS (C1, C2, C3)	22/ 25 (88.0)	52/ 56 (92.9)	4.9	24/25 (96.0)	53/56 (94.6)	-1.4
<b>Baseline HIV-1 RNA (copies/mL)</b>						
<50	126/136 (92.6)	261/280 (93.2)	0.6	129/136 (94.9)	267/280 (95.4)	0.5
>= 50	7/ 12 (58.3)	8/ 15 (53.3)		8/12 (66.7)	12/15 (80.0)	
<b>NVP as the first HAART regimen</b>						
Yes	64/ 73 (87.7)	120/134 (89.6)	1.9	67/73 (91.8)	126/134 (94.0)	2.2
No	69/ 75 (92.0)	149/161 (92.5)	0.5	70/75 (93.3)	153/161 (95.0)	1.7
<b>Duration of previous NVP IR treatment</b>						
<1 year	26/ 30 (86.7)	46/ 52 (88.5)	1.8	27/30 (90.0)	48/52 (92.3)	2.3
1-3 years	36/ 44 (81.8)	92/101 (91.1)	9.3	38/44 (86.4)	96/101 (95.0)	8.6
3-5 years	34/ 35 (97.1)	69/ 75 (92.0)	-5.1	34/35 (97.1)	70/75 (93.3)	-3.8
>5 years	37/ 39 (94.9)	62/ 67 (92.5)	-2.4	38/39 (97.4)	65/67 (97.0)	-0.4
<b>Type of background regimen prior to NVP</b>						
PI based	25/ 28 (89.3)	54/ 58 (93.1)	3.8	26/28 (92.9)	57/58 (98.3)	5.4
NNRTI based	7/ 8 (87.5)	20/ 23 (87.0)		7/8 (87.5)	20/23 (87.0)	
PI based and NNRTI based	11/ 11 ( 100)	26/ 27 (96.3)		11/11 (100)	26/27 (96.3)	
NRTI*	26/ 28 (92.9)	49/ 53 (92.5)	-0.4	26/28 (92.9)	50/53 (94.3)	1.4

\* Previous regimens were NRTI only (ABC, 3TC, and ZDV) or included ABC, 3TC, and ZDV as part of the background

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

A total of 443 subjects were randomized into Study 1100.1526 and received at least one dose of investigational drug: 148 in the nevirapine IR 200 mg BID and 295 in the nevirapine XR 400 mg QD group, respectively. The primary efficacy assessment was based on the non-inferiority analysis of proportion of patients with sustained virologic response (SVR) through Week 24, using LLOQ 50 copies/mL for HIV-1 RNA viral load and included all treated patients in the full analysis set (FAS). Patients who discontinued the study early, or who had viral load missing at Week 24, or whose Week 24 visit were out of the  $24 \pm 4$  weeks window, or who responded earlier and then rebounded, were all considered as virologic failures in the primary efficacy analysis.

At 24 weeks after randomization, sustained virologic response was observed in 137/148 (92.6%) of nevirapine IR patients and 276/295 (93.6%) of nevirapine XR patients, with an observed difference of 1.0% with 95% CI (-4.3%, 6.0%) using the TLOVR algorithm and Amplicor-corrected profile. The observed virologic responder rate was 139/148 (93.9%) in nevirapine IR patients and 281/295 (95.3%) in nevirapine XR patients with a difference of 1.3% and 95% CI (-3.5%, 6.1%) using the SNAPSHOT approach and Amplicor-corrected profile. Nevirapine XR is non-inferior to nevirapine IR according to either a -12% or -10% non-inferiority margin. Secondary analyses of this endpoint using different methods for assaying HIV-1 viral load (TaqMan, Amplicor-corrected), different definitions for HIV-1 viral load suppression ( $\leq 50$  copies/mL,  $\leq 400$  copies/mL), and number of consecutive tests required (SNAPSHOT, TLOVR) confirmed the non-inferiority of nevirapine XR to nevirapine IR.

Similar observations were seen in subgroups by baseline demographics and clinical characteristics. There was some difference observed by background ARV stratum, with an observed difference of -2 to -3% for Truvada® and Combivir® recipients, and +11% for Kivexa®/Epzicom® recipients when comparing nevirapine XR to nevirapine IR. The sponsor's subgroup analysis of sustained virologic response was based on TLOVR algorithm. Additional analysis by this reviewer using SNAPSHOT approach finds no deviation from the above conclusions. Furthermore, a discordance analysis of the TaqMan and Amplicor-corrected methods revealed fairly good agreement between the two assays in testing plasma samples.

A total of 27 patients with detectable HIV-1 viral loads at randomization were enrolled in Study 1100.1526 due to their screening results. Analysis of the primary efficacy endpoints excluding these 27 patients generated consistent findings as those from the entire patient population analysis. The study recruited more patients than initially planned. An additional analysis of sustained virologic response was performed for the first 302 patients randomized in order to assess the impact of over enrollment. The primary efficacy results from the 302 patient population were consistent with the overall results.

## 5.2 Conclusions and Recommendations

For efficacy in Study 1100.1526, low failure rates over 24 weeks were observed in this patient population who entered the study with established virologic suppression. At 24 weeks after randomization, 93.9% and 95.3% of patients receiving immediate-release nevirapine IR 200 mg BID or nevirapine XR 400 mg QD, respectively, continued to have HIV-1 RNA < 50 copies/mL. Treatment with nevirapine XR 400 mg QD was non-inferior to nevirapine IR 200 mg BID: 1.3% more patients responded at Week 24 in favor of nevirapine XR (95% CI [-3.5%, 6.1%]). This finding was consistent across different virologic assays, algorithms for defining virologic response, and analysis data sets. In subgroups with meaningful numbers of patients, there appeared to be no apparent relationship between the proportion of sustained virologic response at Week 24 and any baseline demographics or clinical characteristic, including type of background therapy received.

In conclusion, the results of the 24-week analysis for this trial support the non-inferiority of 400 mg QD nevirapine XR to 200 mg BID nevirapine IR as measured by sustained virologic response and in patients who are stable on the former 200 mg BID nevirapine IR formulation.

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

/s/  
-----

LAN ZENG  
03/02/2011

GUOXING SOON  
03/04/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA

**NDA Number:** 201,152

**Applicant:** Boehringer Ingelheim

**Stamp Date:** 06/03/2010

**Drug Name:** Nevirapine

**NDA/BLA Type:** Standard Review

**Reviewers:** Lan Zeng and Susan Zhou. Ph.D.

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			See C1.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			See C2.

C1. Subgroup analyses were conducted for baseline demographics, characteristics, and lead-in duration. Additionally, the primary efficacy endpoint was analyzed using combinations of different assay profiles, different algorithms to define virologic responders, and different analysis datasets.

C2. SAS \*.xpt files, SAS programs for efficacy analyses can be found in the four subdirectories of NDA201152 (~) in the CDER EDR.

a. For Study 1100.1486, the analysis \*.XPT files (with define.pdf) and SAS programs can be found in ~\0000\m5\datasets\1100-1486\analyses, and raw \*.XPT files (with define.pdf) can be found in ~\0000\m5\datasets\1100-1486\tabulations.

b. Likewise, for Study 1100.1526, the analysis \*.XPT files (with define.pdf) and SAS programs can be found in ~\0000\m5\datasets\1100-1526\analyses, and raw \*.XPT files (with define.pdf) can be found in ~\0000\m5\datasets\1100-1526\tabulations.

c. The HIV-1 viral load data (\*.xpt files and define.pdf) measured by Taqman and Amplicor assays can be found ~\0000\m5\datasets\1100-1486-1100-1526\analyses.

d. SAS programs, \*.XPT file and define.pdf for analyses by sites can be found in ~\0002\m5\datasets\1100-1486\analysis.

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

## STATISTICS FILING CHECKLIST FOR A NEW NDA

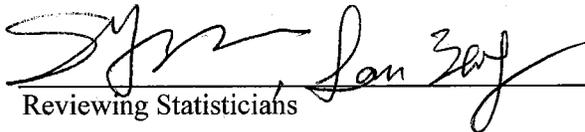
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	See C3.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				See C4.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			See C5.

C3. No formal interim analysis was performed. However, a DSMB periodically reviewed unblinded safety and efficacy data for Study 1100-1486, according to its clinical study report.

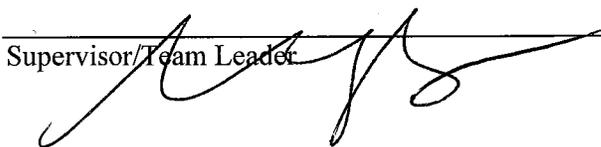
C4. Please refer to the medical reviewer's comments.

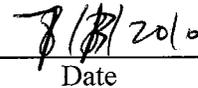
C5. Various methods were used to assess impact of missing data on efficacy endpoints.

  
 \_\_\_\_\_  
 Reviewing Statisticians

July 13, 2010

\_\_\_\_\_  
 Date

  
 \_\_\_\_\_  
 Supervisor/Team Leader

  
 \_\_\_\_\_  
 Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201152	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Nevirapine Extended Release Tablets

---

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

---

/s/

---

SUSAN Y ZHOU  
08/09/2010

LAN ZENG  
08/09/2010

GUOXING SOON  
08/09/2010