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*APPLICATION NUMBER:*  
**201152Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Application Number(s)	201152
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Division / Office	Division of Antiviral Products/Office of New Drugs
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Review Completion Date	February 25, 2011
Established Name	Nevirapine extended-release
(Proposed) Trade Name	Viramune XR
Therapeutic Class	Non-nucleoside reverse transcriptase inhibitor
Applicant	Boehringer Ingelheim
Formulation(s)	Oral tablet
Dosing Regimen	400 mg once daily
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	Adults with HIV-1 infection

Template Version: [March 6, 2009](#)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Approval of this New Drug Application (NDA) for the nevirapine extended-release (XR) tablet is recommended based on review of the safety and efficacy data from two adequate and well-controlled Phase 3 clinical trials. Studies 1100.1486 and 1100.1526 demonstrated the non-inferiority of nevirapine XR 400 mg once daily tablet to the commercially available immediate-release (IR) 200 mg twice daily tablet in achieving sustained virologic response at Week 48 in treatment-naïve HIV-1 infected subjects and at Week 24 in treatment-experienced HIV-1 infected subjects switching from IR to XR. No new potential safety risks were identified in the review and there were no significant issues with the integrity of the submitted data that would preclude this assessment. Although approval of nevirapine XR does not add anything new to the anti-HIV armamentarium, for patients in whom a nevirapine-based antiretroviral regimen is deemed appropriate, the XR formulation will allow for easier once a day dosing and thereby may facilitate greater treatment adherence.

### 1.2 Risk Benefit Assessment

Since the initial approval of nevirapine in 1996, several new antiretroviral (ARV) agents have come to market with improved antiviral potency, a higher barrier to genetic resistance, and a more favorable safety profile than nevirapine. Several of these newer agents are currently listed within the preferred ARV regimens recommended by the U.S. Department of Health and Human Services (DHHS) in the *Guidelines for the Use of Antiretroviral Agents in HIV-1 Adults and Adolescents*.<sup>1</sup> Nonetheless, a nevirapine-based ARV regimen remains listed as an alternative regimen.

The key factors predicting successful therapy with any ARV regimen are adherence to treatment and potency of the regimen. Related to adherence are issues of tolerance and ease of administration. The ability of a nevirapine-based regimen to provide potent and durable virologic suppression has been well established. The important clinical safety concerns with nevirapine are rash and hepatic events and the majority of these events occur early in treatment, within the first 18 weeks. With close monitoring and adherence to prescribed recommendations for initiating nevirapine therapy, including the 14 day lead-in period with once daily nevirapine IR 200 mg and the CD4 cell count thresholds for men and women, nevirapine therapy affords patients safe and effective treatment in combination with other ARV agents. The benefit of a nevirapine extended-release formulation, therefore, is ease of administration. In patients for whom a nevirapine-based regimen is considered appropriate, the nevirapine XR formulation

allows them to combine a once-daily formulation of nevirapine with available once daily formulations of other antiretroviral agents. Studies have shown that once daily regimens are favored by both physicians and patients and result in better adherence and improved long-term outcomes.

In this NDA, nevirapine XR 400 mg once daily was shown to be effective and safe in treatment-naïve subjects, as well as in subjects switched from nevirapine IR 200 mg twice daily (BID). No serious risks were identified with nevirapine XR above and beyond what is already known for nevirapine IR. In fact, there was a trend toward superior safety and efficacy with nevirapine XR. The reasons for this are not entirely clear, as the active ingredient for both formulations is identical. Once nevirapine has been absorbed into the systemic circulation, the pharmacokinetic properties are the same regardless of the formulation. However, in the pivotal trial (Study 1100.1486), subjects treated with nevirapine XR had lower adverse event rates and fewer discontinuations due to adverse events than subjects treated with nevirapine IR. This seemingly greater tolerance with nevirapine XR is perhaps related to its slow and sustained release and absorption properties. Overall, the nevirapine XR formulation resulted in adequate and more uniform plasma concentrations than the twice-a-day nevirapine IR formulation. The slower absorption resulted in less fluctuation of steady state concentrations, which in turn may have led to fewer adverse reactions and greater overall tolerance. Moreover, the relative bioavailability and the safety and efficacy of nevirapine XR were consistent among subjects with different demographics or background ARV therapy.

In conclusion, the benefit of the nevirapine XR tablet is in providing a once a day dosage formulation that results in potentially more effective and safer treatment than the commercially available IR formulation. The nevirapine XR tablet is expected to improve convenience and thereby facilitate treatment adherence. The risk with nevirapine XR is no greater than with the currently approved nevirapine IR formulation and may be slightly less due its sustained release properties.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There are no new recommendations for postmarketing risk management activities in response to this NDA, beyond what is already in place for Viramune® tablets and oral suspension.

The currently approved Risk Evaluation and Mitigation Strategy (REMS) for Viramune® tablets and oral suspension consists of a Medication Guide and timetable for submission of each REMS assessment (December 20, 2009, June 20, 2011, and June 20, 2015). This NDA proposes one combined Medication Guide for all dosage forms of VIRAMUNE (tablets, oral suspension, and extended-release tablets) and combining the

proposed schedule of assessments for VIRAMUNE XR with the existing schedule for immediate-release VIRAMUNE® tablets and oral suspension.

The Medication Guide proposed in this NDA was based on the January 2010 version for Viramune® tablets and oral suspension approved by FDA. However, results of the first REMS assessment in December 2009 indicated that the REMS did not meet its goal. In April 2010, FDA proposed changes to the January 2010 Medication Guide. Discussions are ongoing with FDA's Office of Surveillance and Epidemiology (OSE) regarding these changes and further REMS assessments, which will include a survey of patients' understanding of the potential serious risks of VIRAMUNE. Any changes incorporated into the existing approved Medication Guide will be incorporated into the combined Medication Guide as part of this NDA review.

#### **1.4 Recommendations for Postmarket Requirements and Commitments**

 (b) (4)  
Deferred pediatric studies for subjects 3 to < 18 years of age will be described in a PREA postmarketing requirement. There are no other postmarketing requirements or commitments in response to this application.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependant and DNA-dependant polymerase activities by causing disruption of the enzyme's catalytic site. Nevirapine was the first NNRTI developed and was approved in the U.S. in June 1996 for use in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. The initially approved formulation was the IR tablet, marketed as VIRAMUNE®. An oral suspension formulation was later approved in 1998. Subsequently, the tablet and the oral suspension have been licensed in over 100 countries.

The safety profile of the nevirapine IR formulation is now well established. The expected events of greatest clinical importance are rash and hepatic events. The recommended dose for nevirapine IR is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily. This 2-week lead-in period has been found to lessen the

frequency of rash. In addition, CD4 cell count thresholds have been established for starting nevirapine IR (CD4 cell counts <400 cells/mm<sup>3</sup> for men and <250 cells/mm<sup>3</sup> for women) to decrease the risk of severe and life threatening hepatic events. Given the relative safety issues associated with nevirapine use, a nevirapine-based ARV regimen is currently recommended as an alternative regimen for treatment-naïve patients in the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1 Adults and Adolescents*.<sup>1</sup>

Several published studies have indicated that long term success in anti-HIV therapy is closely related to adherence to treatment and potency of the ARV regimen. In order to increase adherence, once daily treatment regimens are now favored by both physicians and patients.

Boehringer Ingelheim has developed an extended-release oral tablet of nevirapine to be administered as part of a once daily dosing regimen, as an alternative to the commercially available IR twice-daily formulation. In developing the extended-release formulation, the aim was to maintain the efficacy associated with adequate steady state trough plasma levels ( $C_{min,ss} > 3000$  ng/mL).

Nevirapine extended-release tablets are proposed to be marketed under the tradename VIRAMUNE XR.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 24 individual antiretroviral agents approved in the U.S. for treatment of HIV-1 infection. These drugs fall into 5 distinct classes based on their mechanism of action: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry/fusion inhibitors, and integrase inhibitors. In addition, multiple fixed-dose combination tablets containing two or more anti-HIV agents have been approved. A full listing of currently approved anti-HIV medications can be found in the DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1 Adults and Adolescents*.<sup>1</sup> Table 1 below lists the currently available agents in the NNRTI class, which includes nevirapine IR.

**Table 1: Currently Available NNRTIs for Treatment of HIV-1 Infection**

Drug Class	Generic Name	Trade Name	FDA approval date
Non-nucleoside reverse transcriptors (NNRTIs)	Delavirdine (DLV)	Rescriptor	April 4, 1997
	Efavirenz (EFV)	Sustiva	September 17, 1998
	Nevirapine (NVP)	Viramune	June 21, 1996

	Etravirine (ETR)	Intelence	January 18, 2008
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Source: *AIDSinfo.nih.gov*

### **2.3 Availability of Proposed Active Ingredient in the United States**

Nevirapine is currently available in the U.S.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

All of the NNRTIs have the potential to cause hypersensitivity reactions, rash, hepatitis and increased transaminase levels. The risk of any of these events varies with the individual medication; however, the incidence of reported rash and hepatotoxicity has been greatest with NVP.

As a class, the NNRTIs have a relatively low genetic barrier to resistance. Resistance to EFV or NVP is conferred by a single mutation in the reverse transcriptase gene and develops rapidly after virologic failure. Moreover, the mutations that arise often confer cross-resistance within the class. Historically, development of resistance to one agent in the NNRTI class eliminated the entire NNRTI class for use in future combination regimens.

The newest NNRTI etravirine, however, has a higher barrier to resistance and has demonstrated antiviral activity against some isolates with significant mutations that confer resistance to the older NNRTIs. Resistance to etravirine is nonetheless possible with the accumulation of > 3 NNRTI mutations. It has been suggested that treatment failure with NVP may be more likely to lead to ETR-resistance than failure with EFV.<sup>2</sup> Choice of initial NNRTI, therefore, may affect subsequent etravirine response.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The clinical trials for the development of nevirapine XR were conducted under IND 74,744 contingent upon approval from local regulatory agencies in each country. Multiple communications with FDA were had during the course of the development program.

At the End of Phase 2 (September 21, 2007), FDA provided the following comments:

- The Phase 1 Study 1100.1485 (PK), Phase 1 Study 1100.1489 (PK), and Phase 3 Study 1100.1486 are adequate for the filing of a New Drug Application (NDA).
- No drug-drug interaction studies are needed.

At the pre-NDA teleconference (October 19, 2009), FDA requested additional analyses be performed:

- An analysis of the primary endpoint at Week 24 for Study 1100.1526 and at Week 48 for Study 1100.1486 using the supplemental SNAPSHOT methodology provided by the FDA.
- A comparison of viral load assays (Roche Cobas TaqMan assay [TaqMan] and Amplicor) and phenotypic and genotypic resistance testing to nevirapine.
- An analysis of specific drug related adverse events: hepatic events and rash.

Other communications with FDA included the following requests:

Study 1100.1486

- Stratify randomization by baseline HIV-1 viral load ( $\leq 100,000$  copies/mL vs.  $> 100,000$  copies/mL). The analysis of the primary endpoint and key secondary endpoint should be stratified by the baseline viral load stratum.

Study 1100.1526

- The -10% non-inferiority margin was added as a secondary analysis of the primary endpoint.

## 2.6 Other Relevant Background Information

Initial studies for nevirapine XR were conducted in Europe. Following submission of the results of the Phase I Studies 1100.1485 and 1100.1489, the EMA provided the following comments:

- The applicant could proceed with Phase 3 studies.
- Nevirapine IR could be used for the lead-in period for the administration of the XR formulation.
- Pharmacokinetic (PK) differences were observed between the fed and fasted states. Assessment of the clinical relevance could only be based on a controlled study using the IR formulation as an active comparator.
- A bioavailability study and a non-inferiority study may be acceptable to market a new formulation in the EU.

## 3 Ethics and Good Clinical Practices

### **3.1 Submission Quality and Integrity**

In general, the submitted datasets were sufficiently complete and well organized to permit a full review in a timely manner. There were, however, instances where the unique subject identification numbers did not match between different datasets, making the joining or comparison of datasets difficult. The applicant took remedial action by re-submitting the datasets with the same identification numbers for each subject across all datasets.

### **3.2 Compliance with Good Clinical Practices**

The applicant has certified that the clinical trials submitted in support of this NDA were conducted in compliance with principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and in accordance with applicable regulatory requirements.

In the pivotal trial, Study 1100.1486, 45 (4%) subjects had important protocol violations (IR 25 [5%], XR 20 [4%]). The proportion of the protocol violations was comparable between the two treatment groups. The two most common violations were CD4 cell count outside the eligibility criteria at screening (IR 14 [3%], XR 12 [2%]) and poor adherence to medication during the trial (IR 6 [1%], XR 8 [2%]). Other less frequent violations included 4 subjects with resistance to NNRTIs or components of Truvada®; 2 subjects each with previous ARV treatment and lead-in treatment > 28 days; and 1 subject with screening HIV-1 viral load <1,000 copies/mL. Given that the occurrences of these protocol violations were fairly well balanced between the treatment arms, it is unlikely that they affected the integrity of the submitted data.

In the supportive trial, Study 1100.1526, three randomized subjects (IR 1, XR 2) had important protocol violations. Subject 1095 in the NVP IR group and Subject 1080 in nevirapine XR group received less than 18 weeks of nevirapine IR prior to randomization. Subject 2048 in the NVP XR group had a detectable viral load in the four months prior to screening. Given the nature and low numbers of these protocol violations, it is unlikely that they compromised the integrity of the submitted data.

The FDA Division of Scientific Investigations (DSI) audited data from 6 clinical investigators: 5 from Study 1100.1486 in the U.S., Germany, Spain and the U.K.; and 1 from Study 1100.1526 in the U.S. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and site specific protocol violations. Inspection of the U.S. site for Study 1100.1526 (Dr. Douglas Ward) found no violations; inspections of the other 5 sites found violations. Most of the violations were minor and none were considered significant enough to render the data unreliable in support of the application.

### 3.3 Financial Disclosures

The applicant has certified that it has not entered into any financial arrangement with investigators participating in Studies 1100.1486, 1100.1526, and 1100.1489 whereby the value of compensation to the investigator could be affected by study outcome. Certification was available for approximately 94% of investigators participating in the pivotal trial (1100.1486) and 82% of investigators in the supportive trial (1100.1526). In cases where certification was not available, the investigators either did not participate in the trials, were no longer at the study site, or collection of certification was currently in progress. No investigator was identified with disclosable financial interests with Boehringer Ingelheim. The use of randomization in these trials, as well as an objective measure for the primary endpoint (sustained viral response with HIV-1 RNA < 50 copies/mL), reasonably mitigates the potential for bias for financial interest.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The drug substance used in nevirapine XR tablets is identical to that used in the commercial VIRAMUNE® 200 mg IR tablets.

Nevirapine XR 400 mg tablets are yellow, oval, biconvex tablets. The tablets are debossed with product identification “V04” on one side and the Boehringer Ingelheim tower logo on the other side. They are for oral administration. The qualitative and quantitative composition of the nevirapine XR tablet is listed in Table 2. All inactive ingredients are listed in United States Pharmacopoeia - National Formulary and the European Pharmacopoeia.

**Table 2: Qualitative and Quantitative Composition of Nevirapine Extended-Release Tablets (400 mg)**

Name of ingredient	mg per tablet	Function
Nevirapine anhydrous	400.00 mg	Drug substance
Lactose monohydrate		(b) (4)
Hypromellose, (b) (4)		
Iron oxide (b) (4)		
Magnesium stearate		
(b) (4)		
<i>Total weight</i>	1094 mg	

Source: Quality Overall Summary

Lactose and hypromellose (b) (4)

*In vitro* studies were conducted to assess the dissolution profiles of five prototype XR formulations. (b) (4)

Details of these trials can be found in Section 4.4 (Clinical Pharmacology) and Section 5.3 (Clinical Trials). In addition, please see the Chemistry Review by Dr. Shrinkant Pagay.

## 4.2 Clinical Microbiology

Resistance data from the pivotal Phase 3 trial, Study 1100.1486, was submitted with this NDA. Please see the Microbiology Review by Dr. Lalji Mishra for an assessment of the data. In addition, see Section 6.1.10 (Additional Efficacy Issues/Analyses) for a clinical discussion of the findings.

## 4.3 Preclinical Pharmacology/Toxicology

No new nonclinical data was submitted with this application. Previous long-term carcinogenicity studies with nevirapine have indicated an increased incidence of hepatocellular adenomas and carcinomas in mice and rats with nevirapine exposures lower than that measured in humans at the 200 mg BID dose of nevirapine IR. The mechanism of carcinogenic potential is not known and, in the absence of demonstrated genotoxic activity, the relevance if these findings to humans is not clear.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\delta$ ) are not inhibited by nevirapine.

### 4.4.2 Pharmacodynamics

The nevirapine XR formulation contains the same active substance (nevirapine) as nevirapine IR. The pharmacodynamic properties of nevirapine have been extensively

investigated in previous studies with nevirapine IR. Therefore, nevirapine XR is expected to exhibit the same pharmacodynamic effects as nevirapine IR.

Nevirapine XR has slightly lower relative bioavailability (around 80% of AUC) compared to the nevirapine IR tablet. However, the XR tablet provides adequate drug exposure, meeting the target steady state concentrations (trough and  $C_{min,ss}$ ) expected to provide sufficient virologic suppression. In the Phase 3 trials, nevirapine XR demonstrated clinical and virologic efficacy results comparable to nevirapine IR, despite lower exposure concentrations.

#### 4.4.3 Pharmacokinetics

Study 1100.1484 demonstrated that nevirapine can be absorbed throughout the intestinal tract, which makes it suitable for development as a controlled-release formulation that delivers nevirapine slowly over an extended period of time. A series of (b) (4), slow-release NVP 300 and 400 mg prototype tablet formulations were developed and evaluated with different *in vitro* dissolution methods. The *in vitro* dissolution tests concluded that nevirapine was released slowly in a controlled manner by each of these formulations.

The development of an oral XR nevirapine formulation was predicated on maintaining an average steady state minimum plasma concentration ( $C_{min,ss}$ ) around approximately 3,000 ng/mL ( $\pm 500$  ng/mL) with a once daily dosing regimen (although maintenance of a trough concentration above a lowest limit of 1,000 ng/mL should result in no loss of efficacy, based on results from a large clinical trial). Following the single dose evaluation of the *in vivo* performance of 5 different prototype XR formulations in two dose strengths (300 and 400 mg) in healthy male volunteers (Study 1100.1485), two NVP XR prototypes (hypromellose cellulose polymer [KCR] 20% and KCR 25%, each with 300 and 400 mg strengths) were selected for further evaluation. A multiple dose Phase 1b trial using these two prototypes at 300 and 400 mg doses once daily was conducted in HIV-1 infected subjects, with nevirapine IR 200 mg BID as the reference (Study 1100.1489). The effect of a high fat breakfast on the bioavailability of the NVP XR prototypes was also evaluated as part of this trial. (b) (4)

Cumulatively, these early Phase 1 trials demonstrated that the final NVP XR tablet formulation alters the absorption kinetics of nevirapine without affecting the disposition kinetics, either following single dose administration in healthy volunteers or multiple dose administration in HIV-1 infected subjects. NVP XR delivers nevirapine in a slow, controlled manner, resulting in extended absorption along the entire intestinal tract (including the colon) without affecting the PK variability. No dose dumping was observed for NVP XR, neither following single dose nor during multiple administrations. Food co-administration with NVP XR resulted in a slight increase of bioavailability by

approximately 20% for  $AUC_{0-24,ss}$  and  $C_{max,ss}$  without any evidence of dose dumping or increase in variability. The extent of the increase due to a high fat meal was not considered clinically relevant and NVP XR can, therefore, be taken without any food restrictions. Drug metabolism of nevirapine was found to be unchanged independent of the formulation administered (immediate release or XR).

Two Phase 3 trials were conducted using the final 400 mg XR tablet formulation: one randomized, double-blind study in treatment-naïve HIV-1 infected subjects (Study 1100.1486), and one randomized, open-label, parallel group study in subjects already on Viramune® IR (Study 1100.1526). Predose (trough) plasma nevirapine concentrations were obtained along with the viral load data at each visit in each trial. In addition, a PK sub-study with intensive sampling was conducted in Study 1100.1486 for further evaluation of the steady state *in vivo* performance of the final NVP XR drug product in HIV-1 infected subjects.

The PK results from these Phase 3 trials confirm the XR tablet's prolonged release characteristics and also demonstrated that NVP XR is associated with less fluctuation (i.e., lower peak-trough ratio) in the 24 hour PK profile than NVP IR. The Phase 3 trials also showed that the relative bioavailability of NVP XR was consistent among subjects with different baseline demographics or background ARV therapy.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Study number	Study title	Phase
1100.1486	A randomized, double blind, double dummy, parallel group, active controlled trial to evaluate the antiviral efficacy of 400 mg QD neVirapine <b>Extended Release</b> formulation in comparison to 200 mg BID neVirapine <b>E</b> immediate release in combination with Truvada® in antiretroviral therapy naïve HIV-1 infected patients ( <b>VERxVE</b> )	3
1100.1526	An open label, phase 3b, 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 ( <b>TRANxITION</b> )	3b
1100.1489	Steady State Bioavailability of 2 different Nevirapine Extended Release formulations compared to steady state 400 mg of Viramune® (200 mg BID), in HIV-1 infected subjects, an open label, non randomized, multidose and multistage parallel group study ( <b>ERVIR</b> )	1b

Source: Clinical Study Reports (Module 5)

## 5.2 Review Strategy

The Clinical Review of NDA 201,152 was conducted by the Medical Officer (Dr. Peter Miele). This review was based primarily on the 48-week safety and efficacy data from the pivotal Phase 3 trial, Study 1100.1486, which was a randomized, double-blind, non-inferiority trial that compared nevirapine XR 400 mg once daily (QD) tablets to commercially available nevirapine 200 mg BID IR tablets in 1011 treatment-naive HIV-1 infected subjects. Supportive safety and efficacy data were obtained from Study 1100.1526, the Phase 3b open-label, randomized, non-inferiority trial in 443 treatment-experienced, virologically suppressed HIV-1 infected subjects who either switched from nevirapine IR 200 mg BID tablets to nevirapine XR 400 mg QD tablets or remained on their current regimen. Due to the different study populations and designs of Studies 1100.1486 and 1100.1526, efficacy data from the 2 trials were not pooled, but are presented separately by trial. Where appropriate, data from the 2 trials were pooled together for the safety review, but in general the data are presented there separately as well. Dr. Miele was responsible for writing this review. Unless otherwise noted, results reported throughout this review were based on analyses carried out by the Medical Officer (Dr. Miele).

The Clinical Review is complemented by a Statistical Review of primary and secondary efficacy endpoints by Drs. Susan Zhou and Lan Zeng, Mathematical Statistics Reviewers. In addition, resistance data were reviewed by Dr. Lalji Mishra, Microbiology Reviewer; pharmacokinetic considerations were reviewed by Dr. Vikram Arya, Clinical Pharmacology Reviewer; and chemistry issues were reviewed by Dr. Shrinkant Pagay.

## 5.3 Discussion of Individual Studies/Clinical Trials

The three major clinical trials that form the basis of this review are one Phase 1 PK trial, Study 1100.1489, and two Phase 3 trials, the pivotal Study 1100.1486 and the supportive Study 1100.1526. Specifics of each trial are presented below.

### ➤ Study 1100.1489

Study 1100.1489 was a PK trial to evaluate the steady state bioavailability of 2 nevirapine XR prototype formulations using 2 dose levels (KCR 20% and KCR 25%, 300 mg and 400 mg QD) in HIV-1 infected subjects who had been on a stable nevirapine-based (Viramune® 200 mg BID) regimen for at least 12 weeks. The trial was conducted at 20 sites in 4 countries. The baseline steady state PK profile of NVP IR 200 mg BID was compared with the steady state PK profile of each of the 4 XR prototypes. Ninety-two subjects entered into 4 groups of approximately 24 subjects each. Subjects

continued to receive 200 mg BID NVP IR for the first 3 days of the trial, followed by switching to one of the four NVP XR tablet formulations QD under fasting and fed conditions. Trial duration was 22 days and subjects were switched back to NVP IR 200 mg BID at the end.

➤ Study 1100.1486

Study 1100.1486 was a large, Phase 3, randomized, double-blind, parallel-group non-inferiority trial assessing the efficacy and safety of nevirapine XR tablets administered once daily versus nevirapine IR tablets administered twice daily, on a fixed background antiretroviral (ARV) regimen of tenofovir (TDF) and emtricitabine (FTC) (Truvada®) in treatment-naïve, HIV-1 infected subjects. The trial was conducted at 175 sites in 20 countries across 5 continents. Eligible subjects had HIV-1 viral load  $\geq 1000$  copies/mL and adequate renal function (defined as a calculated creatinine clearance  $\geq 50$  mL/min according to the Cockcroft-Gault formula). In addition, eligible male subjects had CD4 cell counts  $> 50$  and  $< 400$  cells/mm<sup>3</sup> and female subjects had CD4 cells counts  $> 50$  and  $< 250$  cells/mm<sup>3</sup>. There were two phases to the trial: an open-label lead-in phase, in which all subjects received treatment with nevirapine IR 200 mg QD for 2 weeks, and a randomized treatment phase in which subjects were randomized 1:1 in a double-blind manner to either nevirapine IR (NVP IR) 200 mg BID or nevirapine XR (NVP XR) 400 mg QD to complete 48 weeks. The lead-in phase could be extended to a maximum of 4 weeks at the discretion of the investigators for subjects who experienced mild or moderate adverse events (AEs) that were considered manageable and not an indication to stop therapy. Total study duration was 48 weeks, with extended treatment up to 144 weeks. Designated trial centers also participated in a PK substudy that included intensive blood collection on Day 28 in 49 subjects.

The primary endpoint of this trial was a sustained virologic response through Week 48, using the lower limit of quantification (LLOQ) of 50 copies/mL for HIV-1 viral load (VL). A virologic response was defined by two consecutive measurements of VL  $< 50$  copies/mL, at least 2 weeks apart. A sustained virologic response had no virologic rebound or change of ARV therapy through Week 48. The time window of Week 48 was defined as  $48 \pm 4$  weeks from Day 1. A virologic rebound was defined by two consecutive measurements of VL  $\geq 50$  copies/mL, at least 2 weeks apart, after a virologic response. If there was unconfirmed change of VL status (rebound or response) at Week 48, then another measurement at least two weeks later was necessary to confirm whether virologic rebound or response had occurred. The HIV-1 assay used for viral load assessment was the Amplicor-corrected assay.

Using a time to loss of virologic response (TLOVR) algorithm, a subject was considered a non-responder or failure at each visit if any of the following events occurred:

- a. Death
- b. Permanent discontinuation of study drug or lost to follow-up

- c. Introduction of a new drug to the regimen
- d. Virologic rebound

In addition to the TLOVR algorithm, a SNAPSHOT method based on FDA input was used to analyze the primary endpoint. According to this method, a subject with a viral load < 50 copies in the Week 48 ± 4 window, using the last viral load measurement if multiple measurements were taken in the window, was defined as a virologic responder. If a subject discontinued prior to the specified window or had a viral load ≥ 50 copies/mL or was missing a viral load in the window, this subject was considered as a failure. A supplemental SNAPSHOT approach, using a broader window (Week 44-54) was also used to evaluate primary endpoint. Using the SNAPSHOT method, virologic outcome at Week 48 was classified by the following categories:

- Virologic Success (Virologic Responder)
- Virologic Failure
- No virologic data in the window:
  - Discontinued study due to AE or death
  - Discontinued study for other reasons
  - Missing data during the window but on study

A key secondary endpoint was the time to loss of virologic response using LLOQ = 50 copies/mL. Other secondary endpoints included virologic response rates at Week 48 using LLOQ = 400 copies/mL, time to loss of virologic response using LLOQ = 400 copies/mL, virologic response at Week 24 and at each visit (LLOQ = 50 copies/mL), time to confirmed virologic response, time to new AIDS or AIDS-related progression event or death, change from baseline in CD4 cell count, and emergence of treatment-related mutations. For the purposes of classifying subjects for whom genotypic testing was conducted, virologic failure was defined as follows: viral load never suppressed, viral load rebound, or viral load partially suppressed. Viral samples successfully amplified were genotyped by (b)(4) using their commercially available (b)(4) assay.

Safety endpoints included adverse events (AEs), investigator-defined drug-related AEs, premature discontinuations due to AEs, serious adverse events (SAEs), rash and hepatic events, and laboratory abnormalities. The trial included the review of data by an independent data safety monitoring board (DSMB).

Changes to the protocol were incorporated by way of 3 amendments. Key changes included: stratification at randomization by baseline HIV-1 viral load, addition of the SNAPSHOT method (see above) as a secondary analysis for the primary endpoint, comparison of virologic response rates at Week 24 between the two groups, and re-assaying of some specimens using the Amplicor assay. (See Section 6.1.1 for further details regarding the re-assaying of virologic samples.)

Study 1100.1486 was powered (90%) to demonstrate non-inferiority (NI) of NVP XR to NVP IR with regard to proportion of responders at Week 48 using -10% NI margin. The planned sample size of n=479 per group had at least 90% of power in order to claim non-inferiority with one-sided alpha = 0.025, assuming expected difference between the two groups is 0 and virologic response rate in both groups was 65%.

See Section 6.1 for a discussion of results from Study 1100.1486.

➤ Study 1100.1526

Study 1100.1526 was an open-label, randomized, parallel-group non-inferiority trial to assess the efficacy and safety of switching treatment-experienced HIV-1 infected subjects from a Viramune® (nevirapine IR, administered 200 mg BID) containing regimen to nevirapine XR 400 mg tablets administered QD. The trial was conducted at 43 sites in 4 countries in Europe and North America. Eligible subjects were treatment-experienced subjects who were already on a nevirapine IR BID regimen with a background therapy of 3TC/ABC (Kivexa® in European Union; Epzicom™ in the U.S., FTC/TDF (Truvada®) or 3TC/AZT (Combivir®) for at least 18 week before study entry and had an undetectable HIV-1 viral load in preceding 1-4 months and at screening. After screening, subjects were randomized in a 2:1 ratio to either switch to NVP XR 400 mg or continue their NVP IR 200 BID therapy, while remaining on their previous background therapy. Study duration was 48 weeks, with extended treatment up to 144 weeks.

The primary endpoint of this trial was virologic response (LLOQ = 50 copies/mL) through Week 24. The Week 24 window was defined as 24 ± 4 weeks from the day a subject started study medication. Proportions of responders through Week 24 were estimated for both treatment groups using TLOVR algorithm and SNAPSHOT approach. A non-inferiority test ( $\Delta = 12\%$ , 10%) was performed by constructing a two-sided 95% CI for the difference in the proportions of virologic response between the two treatment groups for the primary endpoint. Secondary endpoints included time to loss of virologic response, virologic response rates at each visit, and changes from baseline CD4 cell count. Safety endpoints were the same as in Study 1100.1486. Changes to the protocol were made by way of 3 amendments. Key changes included: clarification of treatment failure (subjects who switched background therapies due to toxicity or convenience were not counted as failures), allowing subjects randomized to the NVP IR group to switch to NVP XR at the end of 48 weeks of treatment, re-assaying of specimens with the Amplicor assay( see Section 6.1), and addition of duration of previous NVP use prior to trial.

See Section 6.1 for a discussion of results from Study 1100.1526.

➤ Phase 1 PK trials in healthy volunteers

In addition, data from three other Phase 1 single-dose trials conducted in healthy male volunteers provided PK data and were used to augment the safety database. Please see Section 4.4 of this review and the Clinical Pharmacology Review by Dr. Vikram Arya for further discussion of the PK trial results.

- Study 1100.1484 was a single dose absorption/bioavailability trial to assess the regional absorption of nevirapine following delivery by Enterion™ capsule activation at specific sites (jejunum, ileum, ascending colon, and descending colon). The purpose of this trial was to determine the location of absorption of nevirapine in the intestinal tract to help develop an adequate extended release formulation. The trial demonstrated that nevirapine was absorbed from all 4 sites of the gastrointestinal tract. The rate of nevirapine absorption decreased from jejunum to descending colon and the relative bioavailability decreased in the order of jejunum > ileum > ascending colon > descending colon.
- Study 1100.1485 was a single dose PK study to analyze the PK parameters of 5 different nevirapine XR prototype formulations at 2 different dose strengths. Based on the results of this trial, 2 XR prototype formulations at 300 mg and 400 mg were selected for further evaluation. The 2 formulations were studied in Study 1100.1489 (see above).
- Study 1100.1517 examined the relative bioavailability of a 100 mg nevirapine XR tablet formulation (b) (4)

## 6 Review of Efficacy

### Efficacy Summary

The clinical efficacy review for this NDA is based on data from two Phase 3 clinical trials, the pivotal Study 1100.1486 and the supportive Study 1100.1526. In these trials, 800 HIV-1 infected subjects were treated with the intended-to-be-marketed formulation and dose of the nevirapine oral extended-release tablet (NVP XR 400 mg once daily): 505 HIV-1 treatment-naïve subjects for 48 weeks in Study 1100.1486, and 295 treatment-experienced subjects for 24 weeks in Study 1100.1526. Selection of the formulation and dose used for these Phase 3 trials was based on a multiple-dose Phase Ib study in HIV-1 infected subjects, Study 1100.1489, which evaluated 2 prototype formulations in 2 dose strengths.

Study 1100.1486 evaluated the safety, efficacy, and PK of NVP XR 400 mg compared to commercially available NVP IR 200 mg BID formulation in treatment-naïve subjects. After the initial lead-in treatment with NVP IR 200 mg QD, 1011 subjects (IR 506, XR 505) were randomized and treated with double-blinded study medication for 48 weeks. All subjects received Truvada® as background therapy. Baseline demographics and HIV disease characteristics were comparable between the two randomized treatment groups and were generally representative of a treatment-naïve population. In this trial, 82% of subjects completed the Week 48 visit (IR 81%, XR 83%). For the primary endpoint, virologic response at Week 48 (LLOQ = 50 cells/mL) was observed in 81% of subjects treated with NVP XR and 76% of subjects treated with NVP IR (TLOVR algorithm, Amplicor-corrected HIV-1 RNA assay). The lower bound of the difference was greater than the non-inferiority margin -10%, demonstrating non-inferiority of NVP XR to NVP IR. Using a supplemental SNAPSHOT approach, virologic response rates at Week 48 were 80% for NVP XR vs. 75% for NVP IR. The finding of non-inferiority was consistent regardless of algorithm (TLOVR or SNAPSHOT), HIV-1 RNA assay (Amplicor-corrected or Taqman), or definition of virologic response (LLOQ = 50 or 400 copies/mL).

A trend toward superior efficacy was observed for NVP XR compared to NVP IR at all time points and across multiple subgroup categories. Among subjects with baseline HIV viral load  $\leq$  100,000 copies/mL, virologic response rates were 86% for NVP XR vs. 79% for NVP IR. Loss of virologic response was seen more frequently in the NVP IR group than in the NVP XR group in subjects with baseline viral load  $\leq$  100,000 copies/mL. Among the more difficult to treat population with baseline viral load  $>$  100,000 copies/mL, the difference in virologic response rates was smaller but still favored the NVP XR arm (NVP XR 73% vs. NVP IR 71%). In this population, loss of virologic response was seen at comparable frequencies between the two groups. Time to confirmed virologic response and mean CD4 cell count increases were also comparable.

Study 1100.1526 evaluated the safety and efficacy of switching treatment-experienced subjects from a NVP IR-based regimen to NVP XR 400 mg QD. Baseline demographics and HIV disease characteristics were comparable between the two arms and representative of this population. Subjects entered the trial with established virologic suppression. Randomization was stratified by baseline antiretroviral (ARV) background therapy. Retention in this trial was high, with 98% of subjects reaching the Week 24 visit. For the primary endpoint, virologic response through Week 24 (LLOQ = 50 copies/mL) was observed in 94% of NVP XR subjects and 93% of NVP IR subjects, with a difference of 1% in favor of NVP XR (95% CI: -4.3%, 6.2%), adjusting for baseline background therapy (TLOVR, Amplicor-corrected). NVP XR was non-inferior to NVP IR using either a -12% or -10% non-inferiority margin. This finding was consistent across different virologic assay methods and algorithms. Mean CD4 cell count increases and proportion of subjects who maintained viral load suppression through Week 24 was similar for both treatment groups. No meaningful relationship between baseline factors

and virologic response rates could be determined, although there was some difference observed by background ARV, with an observed difference of -2 to -3% for Truvada® and Combivir® recipients, and +11% for Kivexa®/Epzicom® recipients when comparing NVP XR to NVP IR..

Across both Phase 3 trials, no concentration effect was observed for efficacy in subjects with nevirapine trough concentrations  $\geq 1$   $\mu\text{g/mL}$ .

Based on the analyses for 86 patients with virologic failure who had on-treatment genotyping in Study 1100.1486, the observed mutations at failure were those expected with a nevirapine-based regimen, including Y181C. Two new substitutions were identified: Y181I and Y188N, with resistance to nevirapine confirmed by phenotyping.

In conclusion, data from the Phase 3 trials have demonstrated the non-inferiority of NVP XR to NVP IR, whether in treatment-naïve or nevirapine-experienced subjects. Moreover, there appears to be a trend toward superior efficacy for NVP XR among treatment naïve subjects. These trends were consistent regardless of baseline factors or method of analysis used.

## 6.1 Indication

The proposed indication for the nevirapine XR 400 mg once daily tablet is for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. This is the same indication listed in the U.S. package insert for the commercially available nevirapine IR tablet.

### 6.1.1 Methods

Due to the different study populations and designs of Studies 1100.1486 and 1100.1526, efficacy data from the two trials were not pooled, but presented separately. Common elements to both trials are discussed below.

For both trials, time to loss of virologic response was defined as the time between the start of treatment and confirmed virologic rebound. For Study 1100.1486, time to confirmed virologic response was a secondary endpoint and was defined as the time between the start of lead-in treatment and first viral load  $<$  LLOQ of a confirmed virologic response (2 consecutive measurements of viral load  $<$  LLOQ, at least 2 weeks apart). This endpoint was not applicable for Study 1100.1526, as subjects entering that trial were already confirmed virologic responders.

For Study 1100.1486, the treated set (TS) included all subjects who took at least one dose of study drug, including the lead-in nevirapine treatment. The TS was utilized mostly for the safety evaluation of this review. The full analysis set (FAS), was the

subset of the TS that included all randomized subjects who took at least one dose of randomized (blinded) investigational treatment. This set excluded subjects 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) study drug. In Study 1100.1526, the FAS was the same as the TS as there was no lead-in phase. The FAS was used to conduct the efficacy evaluation, and most of the comparative safety assessment, for Study 1100.1486 in this review.

Prior to the initiation of Studies 1100.1486 and 1100.1526, the supporting central laboratory (b) (4) changed the primary test for HIV-1 viral load quantification from the Roche Cobas Amplicor HIV-1 Monitor version 1.5 Ultrasensitive assay (Amplicor) to the Roche Cobas TaqMan assay (TaqMan). The TaqMan assay was used for measuring HIV-1 viral load for subjects entering these studies. During the conduct of the trials, however, 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. The TaqMan assay appears to detect a higher frequency of results greater than the limit of detection (48 copies/mL) and tends to quantify viral load at a higher value compared with the Amplicor assay, particularly in the critical >48 to 200 copies/mL range. Both Studies 1100.1486 and 1100.1526 were designed based on assumptions of performance for the Amplicor assay. Since the difference in assay performance could impact trial outcome results, backup study samples were re-tested using the Amplicor assay. This re-testing of samples was incorporated into the trials via protocol amendments issued in July 2009, with concurrence from the FDA.

## 6.1.2 Demographics

### Study 1100.1486

The majority of subjects who entered the lead-in phase of Study 1100.1486 were male (85%) and white (75%). The mean age was 38 years old. Half the subjects were from EU sites and 29% from North America and Australia. The majority had baseline HIV-1 RNA levels  $\leq 100,000$  copies/mL and the mean baseline viral load was  $4.68 \log_{10}$  copies/mL. Mean baseline CD4 count was 228 cells/mm<sup>3</sup>. The vast majority of subjects had no history of an AIDS-defining illness and 69% were in a non-AIDS CDC class. Overall baseline demographic and disease characteristics were comparable between the two treatment groups. Baseline characteristics were also generally similar between subjects randomized and not randomized, although the proportions of women, Hispanics, subjects with history of AIDS-defining illness, and subjects with advanced AIDS (CDC class C1, C2, C3) were higher among subjects not randomized. Table 3 provides baseline demographic and disease characteristics for all subjects who entered the lead-in phase (n=1068).

**Table 3: Subject Demographic and HIV Disease Baseline Characteristics (Subjects Entering Lead-In Phase) (Study 1100.1486)**

Baseline characteristic	Not randomized (N=55)	NVP IR 200 mg BID (N=508)	NVP XR 400 mg QD (N=505)	Total (N=1068)
Age (years [mean])	37	38	38	38
<b>Gender</b>				
Male	42 (76)	433 (85)	431 (85)	906 (85)
Female	13 (24)	75 (15)	74 (15)	162 (15)
<b>Race</b>				
White	40 (73)	376 (74)	387 (77)	803 (75)
Black	8 (15)	113 (22)	94 (19)	215 (20)
Asian	7 (13)	13 (3)	15 (3)	35 (3)
Other <sup>a</sup>	0	6 (1)	9 (2)	15 (1)
<b>Hispanic/Latino</b>				
No	41 (75)	399 (79)	390 (77)	830 (78)
Yes	14 (25)	109 (21)	115 (23)	238 (22)
<b>Region</b>				
North America/Australia	14 (25)	150 (30)	141 (28)	305 (29)
Latin America	5 (9)	49 (10)	58 (11)	112 (10)
Europe	32 (58)	252 (50)	257 (51)	541 (51)
Africa	4 (7)	57 (11)	49 (10)	110 (10)
<b>Baseline HIV-1 RNA (log<sub>10</sub> copies/mL) (mean)</b>				
	4.75	4.68	4.67	4.68
<b>HIV-1 RNA stratum (copies/mL)</b>				
≤ 100,000	35 (64)	305 (60)	311(62)	651 (61)
> 100,000	20 (36)	203 (40)	194 (38)	417 (39)
<b>Baseline CD4 count (cells/mm<sup>3</sup>)</b>				
N	55	507	503	1065
Mean	226	228	230	228
<b>Baseline CD4 count categories</b>				
≤ 50	2 (4)	1 (<1)	0	3 (<1)
> 50 - 200	20 (36)	200 (39)	179 (35)	399 (37)
> 200 - 350	30 (55)	263 (52)	282 (56)	575 (54)
> 350 - < 400	2 (4)	31(6)	34 (7)	67 (6)
≥ 400	1 (2)	12 (2)	8 (2)	21 (2)
Missing	0	1 (<1)	2 (<1)	3 (<1)
<b>HIV-1 subtype</b>				
A	9 (16)	37 (7)	30 (6)	76 (7)
B	35 (64)	360 (71)	379 (75)	774 (72)

C	4 (7)	67 (13)	55 (11)	126 (12)
Other	6 (11)	43 (9)	38 (8)	87 (8)
Missing	1 (2)	1 (<1)	3 (1)	5 (1)
History of AIDS-defining illness				
No	49 (89)	482 (95)	475 (94)	1006 (94)
Yes	6 (11)	26 (5)	30 (6)	62 (6)
Lead-in duration (days) (mean)				
	12.8	14.8	14.9	14.7
CDC Class				
Non-AIDS (A1, A2, B1, B2)	37 (67)	347 (68)	357 (71)	741 (69)
AIDS (A3, B3)	14 (26)	141 (28)	130 (26)	285 (27)
AIDS (C1, C2, C3)	4 (7)	20 (4)	18 (4)	42 (4)

<sup>a</sup> Other = American Indian/Alaska native and Hawaiian/Pacific Islander

Source: ADAMEFF, BASCO datasets

### Study 1100.1526

The overall baseline demographic and disease characteristics for subjects in Study 1100.1526 are shown in Table 4. This trial was conducted in Europe and North America only. Compared to the pivotal trial, subjects in the switch trial were older (mean age 47 years) and the proportion of white subjects was higher (92%). In this treatment-experienced population, mean baseline CD4 count was 561 cells/mm<sup>3</sup> and 77% had CD4 counts  $\geq$  400 cells/mm<sup>3</sup>. The vast majority of subjects had undetectable viral load (94%). Subjects with detectable viral loads tended to have HIV-1 RNA values just slightly above cut-off. In addition, most subjects were taking Truvada as background regimen, had no history of AIDS-defining illness, and were in a non-AIDS CDC class. The treatment arms were fairly well balance, although a higher proportion of subjects who had been on previous NVP therapy for 1-3 years were randomized to XR than IR.

**Table 4: Subject Demographic and HIV Disease Baseline Characteristics (Study 1100.1526)**

Baseline characteristic	Number of subjects (%)		
	NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Age (years [mean])	47	47	47
Gender			
Male	128 (86)	244 (83)	372 (84)
Female	20 (14)	51 (17)	71 (16)
Race			
White	134 (91)	270 (92)	404 (92)
Black	13 (9)	20 (7)	33 (7)
Asian	0	5 (2)	5 (1)

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Other <sup>a</sup>	1 (1)	0	1 (<1)
Hispanic/Latino			
No	132 (89)	269 (91)	401 (91)
Yes	16 (11)	26 (9)	42 (9)
Region			
North America	46 (31)	98 (33)	144 (33)
Europe	102 (69)	197 (67)	299 (67)
Baseline HIV-1 RNA (copies/mL)			
< 50	136 (92)	280 (95)	416 (94)
≥ 50	12 (8)	15 (5)	27 (6)
Baseline background regimen			
Truvada®	82 (55)	158 (54)	240 (54)
Combivir®	30 (20)	63 (21)	93 (21)
Kivexa®/Epzicom™	36 (24)	74 (25)	110 (25)
Duration of previous NVP IR therapy			
< 1 year	30 (20)	52 (18)	82 (19)
1 – 3 years	44 (27)	101 (34)	145 (33)
3 – 5 years	35 (24)	75 (25)	110 (25)
> 5 years	39 (26)	67 (23)	106 (24)
Baseline CD4 count (cells/mm <sup>3</sup> )			
N	147	295	442
Mean	567	558	561
Baseline CD4 count categories			
> 50 - 200	2 (1)	6 (2)	8 (2)
> 200 - 350	17 (12)	43 (15)	60 (14)
> 350 - < 400	12 (8)	23 (8)	35 (8)
≥ 400	116 (78)	223 (76)	339 (77)
Missing	1 (1)	0	1 (<1)
History of AIDS-defining illness			
No	118 (80)	221 (75)	339 (77)
Yes	30 (20)	74 (25)	104 (23)
CDC class			
Non-AIDS (A1, A2, B1, B2)	97 (66)	174 (59)	271 (61)
AIDS (A3, B3)	26 (18)	65 (22)	91 (21)
AIDS (C1, C2, C3)	25 (17)	56 (19)	81 (18)

<sup>a</sup> Other = American Indian/Alaska native and Hawaiian/Pacific Islander

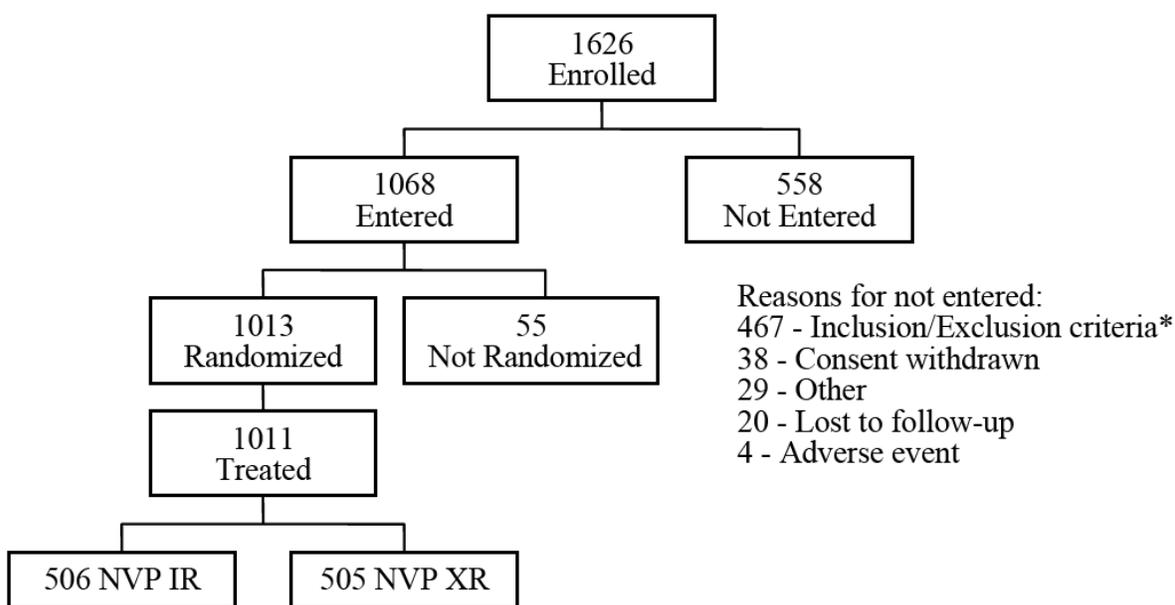
Source: ADAMEFF, BASCO datasets

### 6.1.3 Subject Disposition

#### Study 1100.1486

A total of 1626 subjects enrolled in Study 1100.1486. Of these, 1068 subjects received at least one dose of nevirapine IR QD during the lead-in phase. For the 558 subjects who did not enter the study, the primary reason for exclusion was screen failure (n=467). The most common inclusion and exclusion criteria not met included 213 patients with higher or lower than eligible CD4+ cell counts; 108 with active hepatitis B or C; 69 with elevated laboratory values (DAIDS Grade > 2); 57 with resistance to NNRTIs or one of the components of TRUVADA, and 37 with low HIV-1 viral load <1,000 copies/ml. Other reasons for not entering the study are listed in Figure 1, which also provides a flow chart of subject disposition through the randomization phase of the trial.

**Figure 1: Subject disposition through randomization phase (Study 1100.1486)**



\* Subjects could have multiple inclusion/exclusion failure reasons

Source: Clinical Study Report for Study 1100.1486

Of the 1068 subjects who entered the lead-in phase, 55 (5%) subjects discontinued before randomization, the majority due to adverse events (n=38). The remaining 1013 subjects were randomized to either the nevirapine IR (n=508) or nevirapine XR (n=505) group. Two subjects in the NVP IR group were randomized but never took blinded nevirapine: Subject 14712 withdrew consent because of anticipated travel and Subject 14370 discontinued due to a Grade 2 rash event that occurred in the lead-in phase.

Thus, the total number of subjects randomized and treated in this trial was 1011 (IR 506, XR 505).

Of the 1011 treated subjects, 830 (82%) subjects completed the 48-week visit (IR 409 [81%], XR 421 [83%]), while 181 (18%) subjects discontinued prematurely (IR 97 [19%], XR 84 [16%]). Reasons for discontinuation included 4 deaths (0.4%) (IR 3, XR 1). The remaining discontinuations occurred primarily due to AEs (7% of total) or virologic failure (5%). For any given reason, the proportion of subjects discontinuing prematurely was similar between the two treatment groups, with the exception of 6 cases of pregnancy which all occurred in the NVP XR group. It should be noted that discontinuation due to lack of efficacy was based on investigator discretion. Table 5 provides subject disposition through Week 48, with reasons for early discontinuation.

**Table 5: Subject Disposition through Week 48 (Study 1100.1486)**

	NVP IR 200 mg BID N (%)	NVP XR 400 mg QD N (%)	Total N (%)
Enrolled			1626
Entered lead-in phase			1068
Not randomized			55
Randomized *	508	505	1013
Treated *	506 (100)	505 (100)	1011 (100)
Completed Week 48 visit	409 (81)	421 (83)	830 (82)
Discontinued prior to Week 48 visit	97 (19)	84 (17)	181 (18)
Reasons for discontinuation			
Death	3 (1)	1 (<1)	4 (<1)
Adverse Events	42 (8)	32 (6)	74 (7)
Lost to follow-up	7 (1)	8 (2)	15 (2)
Consent withdrawn	9 (2)	4 (1)	13 (1)
Noncompliance	9 (2)	6 (1)	15 (2)
Lack of efficacy	26 (5)	24 (5)	50 (5)
Pregnancy	0	6 (1)	6 (1)
Other	1 (<1)	3 (1)	4 (<1)

\* Two subjects in the NVP IR group were randomized but not treated with blinded medication  
Source: ADAMEFF dataset

### Study 1100.1526

In Study 1100.1526, a total of 499 subjects enrolled, of whom 445 were randomized and 443 treated. The vast majority (98%) of treated subjects completed 24 weeks (IR 97%, XR 98%). Eleven (2%) subjects discontinued study drug before Week 24 (IR 4 [3%], XR 7 [2%]). The most common reasons for discontinuations were AEs (IR 0, XR 3 [1%]),

followed by lost to follow-up (IR 1 [1%], XR 1 [ $<1\%$ ]) and noncompliance (IR 0, XR 2 [1%]). Table 6 provides subject disposition through Week 24.

**Table 6: Subject Disposition through Week 24 (Study 1100.1526)**

	NVP IR 200 mg BID	NVP XR 400 mg QD	Total
Enrolled			499
Randomized	149	296	445
Treated	148 (100)	295 (100)	443 (100)
Completed Week 24 visit	144 (97)	288 (98)	432 (98)
Discontinued prior to Week 24 visit	4 (3)	7 (2)	11(2)
Reasons for discontinuation			
Death	0	0	0
Adverse events	0	3 (1)	3 (1)
Lost to follow-up	1 (1)	1 ( $<1$ )	2 (1)
Non compliance	0	2 (1)	2 (1)
Consent withdrawn	1 (1)	0	1 ( $<1$ )
Lack of efficacy	1 (1)	0	1 ( $<1$ )
Other	1 (1)	0	1 ( $<1$ )
Pregnancy	0	1 ( $<1$ )	1 ( $<1$ )

Source: ADAMEFF dataset

#### 6.1.4 Analysis of Primary Endpoint(s)

##### Study 1100.1486

The primary endpoint in this trial was virologic response through Week 48 (LLOQ = 50) using the TLOVR algorithm and Amplicor-corrected assay, stratified by baseline HIV-1 viral load. The efficacy dataset submitted with this NDA followed this convention.

Using the submitted efficacy dataset to calculate the Week 48 virologic response rates, 78% of all randomized subjects met the primary endpoint: 81% in the NVP XR group and 76% in the NVP IR group (difference 4.9%, [95% CI -0.1, 10.0]). The difference in response rates between the two treatment arms met the non-inferiority margin prespecified for the trial (-10%). (Please see the Mathematical Statistics review by Dr. Susan Zhou for more detailed analyses of non-inferiority issues.)

When stratified by baseline HIV-1 viral load, the overall proportion of subjects meeting the primary endpoint was higher in subjects with lower baseline viral load ( $\leq 100,000$  copies/mL) than in subjects with higher baseline viral load ( $> 100,000$  copies/mL) (82%

vs. 72%). Comparing treatment arms, the proportion of subjects meeting the primary endpoint was greater in the NVP XR group than in the NVP IR group for subjects with baseline HIV-1 RNA  $\leq$  100,000 copies/mL (86% vs. 79%); the difference in response between the groups was smaller in subjects with baseline viral load  $>$  100,000 copies/mL (73% vs. 71%).

Similar results were seen when the primary endpoint was analyzed using the TLOVR algorithm but with the Taqman HIV-1 RNA assay. Using the Taqman assay, which tends to quantify viral load at a higher value compared with the Amplicor assay and appears to identify a higher frequency of low-level detectable results, resulted in lower rates overall compared to the Amplicor-corrected assay. The treatment effect noted between NVP XR and NVP IR, however, was still observed with the Taqman assay. The difference between the treatment groups was again smaller among subjects with baseline HIV RNA-1 viral load  $>$  100,000 copies/mL.

When the SNAPSHOT method was used to analyze the efficacy dataset, either with the Amplicor-corrected assay or the Taqman assay, the response rates were consistent with the above findings, showing higher response rates in the NVP XR group throughout.

Table 7 presents the proportion subjects with HIV-1 RNA  $<$  LLOQ of 50 copies/mL through Week 48 by TLOVR and SNAPSHOT methods, and by Amplicor-corrected and Taqman-only assays.

**Table 7: Proportion of Virologic Response at Week 48 with LLOQ = 50 copies/mL (Study 1100.1486)**

		Number of responders/total number of subjects (%)		
Analysis method/ HIV-1 Assay	Baseline HIV-1 RNA stratum	NVP IR 200 mg BID	NVP XR 400 mg QD	Total
TLOVR, Amplicor- corrected	$\leq$ 100,000	240/303 (79)	267/311 (86)	507/614 (82)
	$>$ 100,000	144/203 (71)	142/194 (73)	286/397 (72)
	<i>total</i>	384/506 (76)	409/505 (81)	793/1011 (78)
TLOVR, Taqman- only	$\leq$ 100,000	237/303 (78)	256/311(82)	493/614 (80)
	$>$ 100,000	131/203 (65)	130/194 (67)	261/397 (66)
	<i>total</i>	368/506 (73)	386/505 (76)	754/1011 (75)
SNAPSHOT, Amplicor-corrected	$\leq$ 100,000	237/303 (78)	262/311(82)	499/614 (81)
	$>$ 100,000	142/203 (70)	142/194 (73)	284/397 (72)
	<i>total</i>	369/506 (73)	404/505 (80)	783/1011 (77)

SNAPSHOT, Taqman-only	≤ 100,000	234/303 (77)	252/311 (81)	486/614 (79)
	> 100,000	127/203 (63)	125/194 (64)	252/397 (63)
	<i>total</i>	361/506 (71)	377/505 (75)	738/1011 (73)

Source: ADAMEFF dataset

Using the efficacy dataset, the TLOVR algorithm and the Amplicor-corrected assay, 22% of total randomized subjects were classified as failures: NVP IR 24% vs. NVP XR 19%. Virologic failures, defined as subjects who never had viral load suppress through Week 48 and subjects who experienced viral rebound, were seen twice as frequently in the NVP IR group than in the NVP XR group (6% vs. 3%). Among subjects who discontinued therapy before Week 48, the rates due to lack of efficacy (investigator defined) were the same for both treatment groups (5%). A greater proportion of subjects discontinued early due to AEs in the NVP IR group than in the NVP XR group (8% vs. 6%). Table 8 lists the proportion of subjects counted as virologic responders and failures.

**Table 8: Trial Outcomes at Week 48 with LLOQ=50 copies/mL (Amplicor-corrected, TLOVR) (Study 1100.1486)**

Outcome (LLOQ=50 copies/mL)	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Virologic responder	384 (76)	409 (81)	793 (78)
Failures	122 (24)	96 (19)	218 (22)
Virologic failure	30 (6)	16 (3)	46 (5)
Never suppressed through Week 48	13 (3)	5 (1)	18 (2)
Rebound	17 (3)	11 (2)	28 (3)
Discontinued study drug prior to Week 48	92 (18)	80 (16)	172 (17)
Death or events leading to death	3 (1)	1 (<1)	4 (<1)
Adverse events	42 (8)	32 (6)	74 (7)
Lack of efficacy	24 (5)	23 (5)	47 (5)
Loss to follow-up	6 (1)	7 (1)	13 (1)
Consent withdrawn	9 (2)	3 (1)	12 (1)
Noncompliance	7 (1)	5 (1)	12 (1)
Pregnancy	0	6 (1)	6 (1)
Other	1 (<1)	3 (1)	4 (<1)

Source: ADAMEFF dataset

A supplemental SNAPSHOT dataset was also submitted and used to analyze the Week 48 outcomes. This approach used a broader time window (Week 44 to Week 54) for the primary endpoint. The virologic response rates using the SNAPSHOT approach are consistent with the results of the primary analysis above. The results for “virologic

failures” are slightly different, however, but may be accounted for by subjects who discontinued prior to Week 48 as these subjects are categorized differently in each algorithm. Table 9 lists the results of the SNAPSHOT analysis for the primary endpoint. This table will be used in drafting the U.S. package insert (USPI) label for nevirapine extended-release tablets.

**Table 9: Trial Outcomes at Week 48 Window (44-54 weeks) with LLOQ=50 copies/mL (Amplicor-corrected, SNAPSHOT) (Study 1100.1486)**

Outcome (SNAPSHOT)	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Virologic success	380 (75)	405 (80)	785 (78)
Virologic failure	67 (13)	54 (11)	121 (12)
No virologic data at Week 48 window	59 (12)	46 (9)	105 (10)
Discontinued study due to AE or death	45 (9)	33 (7)	78 (8)
Discontinued study for other reasons	13 (3)	13 (3)	26 (3)
Missing data during window but on study	1 (<1)	0	1 (<1)

Source: SNAPSHOT dataset

### Study 1100.1526

In Study 1100.1256, the primary efficacy endpoint was virologic response through Week 24 using LLOQ=50 copies/mL (TLOVR algorithm, Amplicor-corrected assay). The primary analysis was the test of non-inferiority of NVP XR compared to NVP IR (NI margin = -12% or -10%), stratified by background therapy.

Overall, 93% of treated subjects met the primary endpoint (IR 93%, XR 94%). The adjusted overall difference between the two treatment groups was 1% (95% CI -4.3%, 6.2%). Among subjects with Truvada® or Combivir® background therapy, the proportions of subjects reaching the primary endpoint were slightly higher in the NVP IR group than in the NVP XR group, but among subjects taking Epzicom™ background therapy the proportion was higher in the NVP XR group (difference of 11%). It is not clear why subjects taking Epzicom™ had lower response rates with NVP IR (86%) compared to NVP XR (97%) or subjects taking other NRTI regimens (95%). Table 10 lists overall response rates and by background therapy.

**Table 10: Proportion of Virologic Response at Week 24 with LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR) (Study 1100.1526)**

	Number of responders/total number of subjects (%)		
	NVP IR 200 mg BID	NVP XR 400 mg QD	Total
Total	137/148 (93)	276/295 (94)	413/443 (93)

Background regimen			
Truvada®	77/82 (94)	145/158 (92)	222/240 (93)
Combivir®	29/30 (97)	59/63 (94)	88/93 (95)
Kivexa®/Epzicom™	31/36 (86)	72/74 (97)	103/110 (94)

Source: ADAMEFF dataset

Using the TLOVR algorithm and the Amplicor-corrected assay, and excluding subjects who discontinued therapy prior to Week 24 (IR 3 [2%], XR 7 [2%]), there were 20 subjects who experienced virologic failure in this trial (IR 8 [5%], XR 12 [4%]). Of these, 15 subjects had viral rebound (IR 5 [3%], XR 10 [3%]). The other 5 had Week 24 visits outside the visit window or had missing values for the window and were therefore counted as failures.

Secondary analyses of the primary endpoint were conducted using the TLOVR algorithm and TaqMan-only assay and using the SNAPSHOT method with both the Amplicor-corrected assay and with the TaqMan-only assay. Results of these analyses (not shown) also demonstrated the non-inferiority of NVP XR to NVP IR in this switch trial.

As was done for Study 1100.1486, a supplemental SNAPSHOT analysis was conducted for Study 1100.1526 using a broader time window for Week 24 (18-30 weeks) (Table 11). The virologic success rates obtained with this method are similar to the results obtained with the primary analysis. Again, the rates of virologic failure are slightly different compared to the TLOVR method since subjects with no data in the window are counted separately, but the relative proportions of non-responders between the two treatment groups remain consistent.

**Table 11: Trial Outcomes at Week 24 window (18-30 weeks) with LLOQ=50 copies/mL (Amplicor-corrected, SNAPSHOT) (Study 1100.1526)**

Outcomes (SNAPSHOT)	Number of subjects (%)		
	NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Virologic success	139 (94)	283 (96)	422 (95)
Virologic failure	3 (2)	5 (2)	8 (2)
No virologic data in Week 24 window	6 (4)	7 (2)	13 (3)
Discontinued study due to AE or death	0	3 (1)	3 (1)
Discontinued study for other reasons	3 (2)	4 (1)	7 (2)
Missing data during window but on study	3 (2)	0	3 (1)

Source: SNAPSHOT dataset

### 6.1.5 Analysis of Secondary Endpoints(s)

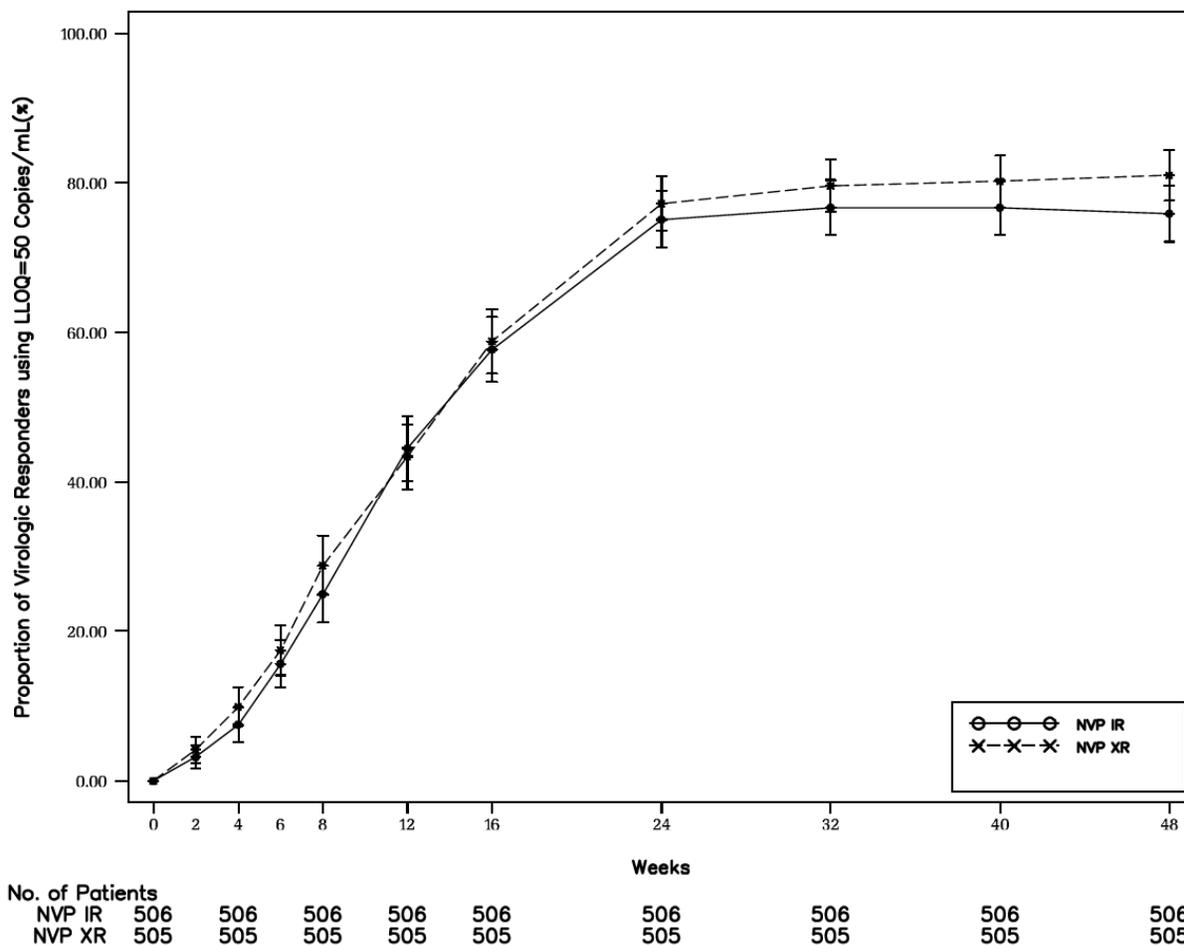
#### Study 1100.1486

Based on Kaplan-Meier curves conducted by the applicant (not shown), the time to confirmed virologic response (LLOQ = 50 copies/mL, Amplicor-corrected) was comparable between the two treatment groups. These findings were seen with the Taqman-only assay as well. The NVP XR group, however, had greater proportions of subjects without loss of virologic response (using LLOQ = 50 copies/mL, Amplicor-corrected assay) at all time points through Week 72 among subjects with baseline viral load  $\leq 100,000$  copies/mL. For subjects with baseline viral load  $> 100,000$  copies/mL, the proportions of subjects without loss of virologic response were comparable between the two treatment groups. Similar trends were observed with the TaqMan assay as well.

The NVP XR group also had a higher proportion of subjects with virologic response (LLOQ = 50 copies/mL) than the NVP IR group at Week 24 (TLOVR algorithm, Amplicor-corrected assay) (IR 380 [75%], XR 390 [77%]). This finding persisted regardless of algorithm (TLOVR or SNAPSHOT) or HIV-1 RNA assay (Amplicor-corrected or TaqMan-only) employed. In addition, the NVP XR group had a higher proportion of subjects with virologic response at Week 48 using LLOQ = 400 copies/mL (TLOVR algorithm) (IR 399 [79%], XR 420 [83%]). This finding was also seen with the SNAPSHOT algorithm.

Overall, the NVP XR group tended to have a higher response rates than the NVP IR group at multiple time points from Week 2 to Week 48 (Figure 2).

**Figure 2: Proportion of virologic response using LLOQ=50 copies/mL by visit (Amplicor-corrected, TLOVR) (Study 1100.1486)**



| bar represent 95% confidence intervals

Source: Clinical Study Report for Study 1100.1486

CD4 cell counts increased rapidly from baseline in the first 8 weeks for both treatment groups in this trial. At Week 48, the mean increase was +181 and +192 cells/mm<sup>3</sup> for NVP IR and NVP XR, respectively. In general, when adjusted for baseline HIV-1 viral load stratum, the increase in CD4 cell count for the two treatment groups was similar at Week 48, whether using observed or last-observation-carried-forward (LOCF) values.

### Study 1100.1526

In this switch trial, subjects entered the trial with HIV-1 viral load < 50 copies/mL. The proportion of subjects who maintained virologic response (Amplicor-corrected assay) was similar for both treatment groups through Week 24. No significant difference was

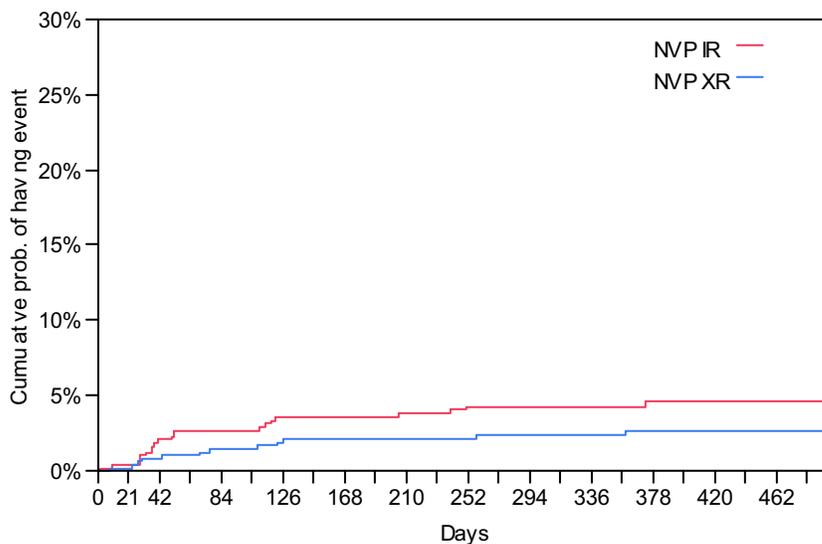
noted between the two groups in time to loss of virologic response, based on Cox model and adjusted for background ARV therapy (per analyses done by applicant). Overall, there was slight and gradual decrease in the proportion of responders at each visit through Week 24, with little difference between the two groups.

At Week 24, the mean CD4 cell count increase was +50 and +45 cells/mm<sup>3</sup> for the NVP IR and NVP XR groups, respectively. These findings were consistent whether using observed or LOCF values.

### 6.1.6 Other Endpoints

In Study 1100.1486, 31 (3%) of 1011 treated subjects had new AIDS events (IR 19 [4%], XR 12 [2%]). In addition, there were two AIDS-related deaths in the NVP IR group versus none in the NVP XR group. Per Kaplan-Meier curves (Figure 3), the cumulative probability of having a new AIDS or AIDS-related progression event or death was comparable between the two groups during the first 6 weeks, but the probability tended to be higher for the NVP IR group than the NVP XR group from Week 6 to Week 72.

**Figure 3: Kaplan-Meier curves for time to new AIDS or AIDS-related progression event or death (Study 1100.1486)**



Source: TIMEV dataset

### 6.1.7 Subpopulations

#### Study 1100.1486

Using the TLOVR algorithm and Amplicor-corrected assay, there appeared to be no relationship between virologic response at Week 48 and age group, gender, race, ethnicity, or region (Table 12). Subjects > 55 years of age had lower response rates overall than younger subjects, but the rates were comparable between treatment arms. Subjects who identified as American Indian/Alaska native or Hawaiian/Pacific Islander had lower response rates in the NVP XR group compared to similar subjects in NVP IR group and subjects of other races, but the total number of subjects in this category was very small.

As noted previously, subjects with lower baseline HIV-1 RNA ( $\leq 100,000$  copies/mL) had higher Week 48 response rates overall than subjects with baseline viral load  $> 100,000$  copies/mL. The virologic response rates, however, were higher in the NVP XR group compared to the NVP IR group regardless of baseline HIV-1 viral load stratum. Among CD4 cell count categories with meaningful sample size, there appeared to be no relationship between baseline CD4 cell count and virologic response, although again the rates were higher in the NVP XR group across CD4 categories. There was no discernable pattern observed for the relationship between HIV-1 subtype and virologic response. Among subjects with HIV-1 subtype A infection, however, the response rate in the NVP XR group was lower compared to the NVP IR group and compared to subjects with other subtypes, but the total number of subjects in this subgroup was relatively small. For both the CDC Non-AIDS (A1, A2, B1, B2) and AIDS (C1, C2, C3) classes, the proportion of virologic responders was higher in the NVP XR group than in the NVP IR group. The response rates were comparable between the two treatment groups for the AIDS A3,B3 sub-group. Lastly, there was no discernible relationship between duration of lead-in treatment and proportion of virologic responders.

Table 12 lists the virologic response rates at Week 48 by baseline demographics and HIV-1 disease characteristics.

**Table 12: Proportion of Virologic Response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR) by Baseline Demographic and Disease Characteristics (Study 1100.1486)**

Subgroup		Number of responders/total number of subjects (%)		
		NVP IR 200 mg BID	NVP XR 400 mg QD	Total
Total		384/506 (76)	409/505 (81)	793/1011 (78)
Age (years)	18 - 40	235/314 (75)	242/300 (81)	477/614 (78)

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	41 - 55	129/165 (78)	149/181 (82)	278/346 (80)
	> 55	20/27 (74)	18/24 (75)	38/54 (70)
Gender	Male	329/431 (76)	353/431 (82)	682/862 (79)
	Female	55/75 (73)	56/74 (76)	111/149 (75)
Race	White	285/374 (76)	321/387 (83)	606/761 (80)
	Black	84/113 (74)	72/94 (77)	156/207 (75)
	Asian	10/13 (77)	11/15 (73)	21/28 (75)
	Other	5/6 (83)	5/9 (56)	10/15 (67)
Ethnicity	Hispanic/Latino	82/108 (76)	96/115 (84)	178/223 (80)
	Not Hispanic/Latino	302/398 (76)	313/390 (80)	615/788 (78)
Region	North America/Australia	114/148 (77)	114/141 (81)	228/289 (79)
	Europe	185/252 (73)	204/257 (79)	389/509 (76)
	Latin America	39/49 (80)	51/58 (88)	90/107 (84)
	Africa	46/57 (81)	40/49 (82)	86/106 (81)
Baseline HIV-1 RNA	≤100,000	240/303 (79)	267/311 (86)	507/614 (83)
	> 100,000	144/203 (71)	142/194 (73)	286/397 (72)
Baseline CD4 cell count (cells/mm <sup>3</sup> )	≤ 50	0/1 (0)	0	0/1 (0)
	> 50 - 200	144/199 (72)	137/179 (77)	281/378 (74)
	> 200 - 350	208/263 (79)	236/282 (84)	444/545 (81)
	> 350 - < 400	24/31 (77)	27/34 (79)	51/65 (78)
	≥ 400	7/11 (63)	7/8 (88)	14/19 (74)
	Missing	1/1 (100)	2/2 (100)	3/3 (100)
HIV-1 subtype	A	30/37 (81)	20/30 (67)	50/67 (75)
	B	272/358 (76)	314/379 (83)	586/737 (80)
	C	52/67 (78)	43/55 (78)	95/122 (79)
	Other	29/43 (67)	29/38 (76)	58/81 (72)
	Missing	1/1 (100)	3/3 (100)	4/4 (100)
CDC class	Non-AIDS (A1, A2, B1, B2)	266/354 (77)	298/357 (85)	564/702 (80)
	AIDS (A3, B3)	104/141 (74)	95/130 (73)	199/271 (73)
	AIDS (C1, C2, C3)	14/20 (70)	16/18 (89)	30/38 (79)

Source: ADAMEFF, BASCO datasets

### Study 1100.1526

Based on the Amplicor-corrected assay and LLOQ = 50 cells/mL, there did not appear to be a relationship between virologic response and such intrinsic factors as gender, race, ethnicity, or region for either treatment group in Study 1100.1526 (data not shown). Overall, the NVP XR group tended to have slightly higher response rates than the NVP IR group for each subgroup having a sizeable number of subjects.

Since the mean age of the population in this trial was older than in the pivotal trial, an analysis of virologic response based on age was carried out (Table 13). Among middle aged subjects (41-55 years old), response rates between the 2 treatment groups were identical (95%). However, among young adults (18-40 years old), response rates were higher in the NVP XR group than in the NVP IR group (91% vs. 83%). The opposite was seen among older subjects (> 55 years old), where the NVP IR group had higher rates than the NVP XR group. The total number of subjects in the younger and older categories, however, was relatively small compared to the middle aged cohort.

As the population in this trial was also treatment-experienced, certain baseline treatment characteristics were analyzed to evaluate for an effect on virologic response. As previously noted, no conclusive relationship was noted between concomitant background NRTI therapy and response, as the overall proportions of virologic responders at Week 24 were comparable among the 3 background regimens (Table 10). Similarly, the type of previous HARRT regimen (PI-, NNRTI-, or NRTI-based) had no effect on virologic response. In addition, there was no apparent effect seen among subjects with a NVP-based regimen as their first ARV treatment. Interestingly, however, there were some findings noted for duration of previous NVP therapy. Among subjects on NVP for > 3 years at study entry, the proportion of responders was slightly higher in the NVP IR group than in the NVP XR group (IR 97%, XR 94%), whereas among subjects on NVP ≤ 3 years, the opposite was observed (IR 88%, XR 93%). The significance of these findings is not clear, and the differences are small, but they might suggest that subjects relatively new to NVP IR therapy might have better response rates with the XR formulation.

For CDC class, virologic response rates were generally similar between the two treatment groups, with the exception of subjects with AIDS class A3, B3, where subjects in the NVP IR had significantly lower rates than the NVP XR group (77% vs. 92%). Likewise, the NVP IR group had lower response rates among subjects with baseline CD4 cell count between 200 and 350 cells/mm<sup>3</sup> (65% vs. 93%). However, the number of NVP IR subjects within these subgroups was small, making it difficult to draw meaningful conclusions.

**Table 13: Proportion of Virologic Response at Week 24 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR) by Select Baseline Characteristics (Study 1100.1526)**

Subgroup		Number of responders/total number of subjects (%)		
		NVP IR 200 mg BID	NVP XR 400 mg QD	Total
Age (years)	18 - 40	30/36 (83)	64/70 (91)	94/106 (87)
	41 - 55	75/79 (95)	160/168 (95)	235/247 (95)
	> 55	32/33 (97)	52/57 (91)	84/90 (93)
Baseline CD4 cell count	> 50 – 200	2/2 (100)	6/6 (100)	8/8 (100)
	> 200 - 350	11/17 (65)	40/43 (93)	51/60 (85)
	> 350 - < 400	11/12 (92)	21/23 (91)	32/35 (91)
	≥ 400	112/116 (97)	209/223 (94)	321/339 (95)
	Missing	1/1 (100)	--	1/1 (100)
CDC class	Non-AIDS (A1, A2, B1, B2)	93/97 (96)	163/174 (94)	256/271 (95)
	AIDS (A3, B3)	20/26 (77)	60/65 (92)	80/91 (89)
	AIDS (C1, C2, C3)	24/25 (96)	53/56 (95)	77/81 (95)
Duration of previous NVP IR treatment	< 1 year	27/30 (90)	49/52 (94)	76/82 (93)
	1 - 3 years	38/44 (86)	94/101 (93)	132/145 (91)
	3 - 5 years	34/35 (97)	70/75 (93)	104/110 (95)
	> 5 years	38/39 (97)	63/67 (94)	101/106 (95)

Source: ADAMEFF, BASCO datasets

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In developing a nevirapine extended-release formulation, the applicant sought to study formulations with steady state PK profiles with lower maximum plasma concentrations ( $C_{max}$ ) and moderately lower exposures (area under the curve [AUC]) than the currently commercially available IR tablet. A  $C_{min}$  of  $3 \pm 0.5 \mu\text{g/mL}$  was considered the target for efficacy and safety. Selection of the formulation and dose for the NVP XR tablet was based on the results of Study 1100.1489, which will be discussed in this section. In addition, please see the review by Dr. Vikram Arya, Clinical Pharmacology, for a detailed discussion of the PK data submitted in support of this NDA.

Study 1100.1489 was a PK trial in HIV-1 infected subjects that compared the steady-state bioavailability of NVP IR 200 mg BID to four NVP XR formulations: 400 mg QD KCR 25%, 400 mg QD KCR 20%, 300 mg QD KCR 25%, and 300 mg QD KCR 20% (see Section 5.3 of this review for trial design details). The bioavailability and rate of absorption for all four NVP XR formulations was found to be lower than for NVP IR. The

PK parameters for all NVP XR formulations were moderately higher under fed conditions compared with fasting, but were still slightly below nevirapine IR exposures. The KCR 25% formulations, however, had better relative bioavailability than the KCR 20% formulations. Also, the observed difference in  $C_{min}$  parameters between the NVP XR 400 mg KCR 25% formulation and NVP IR was smaller than the difference between NVP XR 400 mg KCR 20% and NVP IR in the same subjects. This same pattern held for  $C_{min,ss}$  geometric means for both 400 mg formulations. Both 300 mg formulations, on the other hand, resulted in  $C_{min,ss}$  levels that were lower than the target level considered necessary for efficacy. All NVP XR formulations were safe and well tolerated in this trial. The mean viral load remained at or below the level of detection throughout treatment, and no virological failures were observed. (b) (4)

In the Phase 3 trials (Studies 1100.1486 and 1100.1526), the effects of trough concentration on primary endpoints were evaluated using geometric means of all available steady-state troughs for each subject, from Weeks 4 to 48 in Study 1100.1486 and from Weeks 2 to 24 in Study 1100.1526. Overall, no effect was observed in either trial between nevirapine trough concentrations and virologic response for trough levels above 1 µg/mL. Moreover, there were no race, gender, or region interactions between trough levels and virologic response rates. These findings, in combination with the overall efficacy results observed in the Phase 3 trials, suggest that treatment with NVP XR 400 mg QD was effective despite exposures that were lower than NVP IR treatment.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See above, Section 6.1.8.

#### 6.1.10 Additional Efficacy Issues/Analyses

Genotypic and phenotypic resistance testing were performed in a selected subgroup in Study 1100.1486. The results of these analyses will be discussed briefly in this section. For a more detailed discussion of the resistance data submitted with this application, please see the Microbiology Review by Dr. Lalji Mishra.

A total of 86 subjects in Study 1100.1486 had on-treatment samples selected for genotypic testing (IR 54, XR 32). Table 14 lists the virologic failure classifications for the 86 subjects selected for genotypic testing. Of note, 4 these subjects (IR 3, XR 1) were actually responders at Week 48 but had a transient increase in viral load during the course of the trial, and thus, had genotypic testing performed. Also, the majority of these subjects (65%) had baseline viral load > 100,000 copies/mL.

**Table 14: Summary of Subjects Selected for Genotypic Testing (Study 1100.1486)**

Viral failure classification	NVP IR 200 mg BID	NVP XR 400 mg QD	Total
Total number genotyped	54	32	86
Week 48 responders	3	1	4
Discontinued study drug due to reasons other than efficacy; e.g., AE, noncompliance	18	10	28
Partial responder	13	10	23
Early rebounder ( $\leq$ Week 16)	14	8	22
Late rebounder ( $>$ Week 16)	6	3	9

Source: Microbiology Review

Of the 86 subjects with genotypic testing, 36 (42%) did not have resistant virus at the time of failure. All of the remaining 50 (58%) subjects had resistance to nevirapine, and 43 (50%) had resistance to FTC. Tenofovir resistance was seen in 13 (15%) subjects; these subjects also had resistance to NVP and FTC. Overall, the patterns of resistance were comparable between both treatment groups.

When cross resistance among the more widely used NNRTIs (NVP, efavirenz [EFV], etravirine [ETR]) was evaluated, no difference in resistance patterns was noted between the two treatment groups. Etravirine resistance was observed in 5 subjects who had not developed nevirapine resistance, although in at least 1 of these cases, there was phenotypic evidence of ETR resistance at baseline. Of the 50 subjects with NVP-resistant virus at failure, 22% (11/50) were also resistant to EFV but not ETR (Y188N substitution), 44% (22/50) were also resistant to ETR but not EFV (Y181I substitution), and the remaining 34% (17/50) were resistant to all 3 NNRTIs (Y188C plus M230L). Both Y181I and Y188N substitutions were observed for the first time in this trial to confer reduced susceptibility to NVP. However, Y181I has been previously shown to confer reduced susceptibility to ETR.

The observed mutations were mostly those that would be expected according to the current nevirapine label and the International AIDS Society (IAS) list of nevirapine-associated mutations. The most common amino acid substitution was Y181C. Two new amino acid substitutions associated with nevirapine failure were identified in these analyses: Y181I and Y188N. Subjects with these substitutions had substantial decreases in NVP susceptibility. Phenotypic testing confirmed that these emergent mutations were associated with resistance. By contrast, several NNRTI mutations on the IAS list were not found to affect the clinical response to nevirapine, despite being associated with resistance to ETR. Overall, no difference in resistance was observed related to formulation type (IR or XR).

## 7 Review of Safety

### **Safety Summary**

The safety review for this NDA is based on safety data from 800 HIV-1 infected subjects administered the oral NVP XR tablet with the final formulation and intended marketed dose (400 mg QD). These data were collected from two Phase 3 trials, the pivotal Study 1100.1486 and the supportive Study 1100.1526. In these trials, 505 HIV-1 treatment-naïve subjects received at least 48 weeks, and 295 treatment-experienced subjects received at least 24 weeks of NVP XR 400 mg QD.

Study 1100.1486 evaluated the safety, efficacy, and PK of NVP XR 400 mg compared to the commercially available NVP IR 200 mg BID in treatment-naïve subjects. After the initial lead-in treatment with NVP IR 200 mg QD (n=1068), 1011 subjects (IR 506, XR 505) were randomized and treated with blinded medication for 48 weeks. All subjects received Truvada® as background therapy. Baseline demographics and HIV disease characteristics were comparable between the randomized treatment arms and representative of a treatment-naïve population. Fifty-five (55) of 1068 subjects discontinued the trial during the lead-in phase; 38 of these discontinued study drug due to AEs, primarily rash, consistent with the NVP IR label. Two subjects in the lead-in experienced Stevens-Johnson syndrome (SJS). In the randomized phase, 77 of 1011 subjects discontinued study medication early due to AEs (IR 45, XR 32). The most common AEs leading to study drug discontinuation were rash (including SJS), increased transaminases, hepatotoxicity, and nausea. Overall, AE rates were generally comparable between the two treatment groups. For certain AE categories, however, the frequencies were slightly higher in the NVP IR group compared to the NVP XR group: AEs leading to discontinuation (9% vs. 6%), drug-related AEs of at least moderate intensity (DAIDS Grade  $\geq 2$ ) (13% vs. 11%), and hepatic AEs (4% vs. 2%). The frequencies for serious AEs (SAEs), rash events, and common AEs were similar between the two groups. However, for Grade 3/4 rash events, the frequencies were again slightly higher in the NVP IR group; moreover, the 3 cases of SJS reported during the randomized phase all occurred in the NVP IR group. The most frequently reported SAEs were pneumonia, depression, and Kaposi's sarcoma, each reported in 5 subjects (IR 3, XR 2). The number of SAEs related to rash or hepatotoxicity was small, but balanced between the two groups. Laboratory abnormalities encountered in this trial were mostly Grade 2; the overall rates of laboratory abnormalities (including lipids) were comparable between the two groups. There were 10 deaths, 6 of which occurred after randomization (IR 5, XR 1). None of the deaths were related to treatment.

Study 1100.1526 evaluated the safety and efficacy of switching treatment-experienced subjects from a NVP IR-based regimen to NVP XR 400 mg QD. Baseline demographics and HIV disease characteristics were comparable between the two treatment arms and

representative of this population. Subjects who entered the trial had demonstrated tolerance to nevirapine therapy. Retention in this trial was high (98%), with only 3 subjects discontinuing study medication (XR 3) before Week 24. As might be expected in a switch trial, the proportion of subjects reporting any AE was higher in the NVP XR group than in the NVP IR group (76% vs. 60%). This finding extended to most categories: SAEs (6% vs. 3%), AEs leading to discontinuation (1% vs. 0), and drug-related AEs of any severity (12% vs. 2%). It should be noted, however, that none of the SAEs encountered among the NVP XR group were considered drug-related by the investigator. Moreover, the number of AEs leading to discontinuation in the NVP XR group was small (n=3), only 2 of which were investigator-defined drug-related. Lastly, the majority of drug-related AEs in the NVP XR group were Grade 1; drug-related AEs of at least moderate severity (DAIDS Grade  $\geq 2$ ) were limited in this trial and balanced between the two groups. The leading drug-related AEs in the NVP XR group were fatigue, nausea, and diarrhea. There were a total of 3 rash events and no hepatic events reported in this trial. The 3 rash events (2 mild, 1 moderate) all occurred in the NVP XR group. Laboratory abnormalities were not a significant finding in this trial and there were no deaths reported.

Pooling of data from the two trials was generally avoided given the different study designs and populations. However, when all AEs were pooled together, no new safety findings emerged. The frequency of overall rash events was consistent between the two treatment groups; however, for severe or life-threatening rash or SJS, the rates were higher in the NVP IR group. Hepatotoxicity was also more frequently encountered in the NVP IR group. Drug-demographic and drug-disease (i.e., baseline CD4 cell count) analyses were consistent with the known safety profile of nevirapine. The probability of developing a rash or hepatic event was higher for women than men, and higher for women in the NVP IR group than in the NVP XR group. AE rates observed in subgroups defined by race or region were generally consistent with those observed for the overall study population.

The safety database was augmented by data from four Phase 1 trials conducted in healthy volunteers (n=327) and HIV-1 infected subjects (n=24) to characterize the bioavailability and PK of NVP XR. No new or unexpected AEs were observed in these Phase 1 trials.

Reports of drug remnants in subjects' stools were noted from multiple investigator sites across both trials. The occurrence of these events was rare (2%) and the findings did not have a noticeable impact on either drug exposures or virologic response.

Overall, the safety review for this NDA did not identify any new findings not previously known to be associated with nevirapine use. The NVP XR tablet appears to be as safe and well tolerated as the commercially available IR formulation in treatment-naïve subjects, and for some significant events (hepatic injury, severe rash) and in some instances (e.g. treatment in women) may be associated with less toxicity. Likewise,

switching treatment-experienced subjects from NVP IR to NVP XR does not appear to be associated with any increase in major toxicity.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Data from the two Phase 3 clinical trials, the pivotal Study 1100.1486 and the supportive Study 1100.1526, form the basis of this safety review. Details of each trial design can be found in Section 5.3 of this review. The Week 48 safety data were used for Study 1100.1486 and Week 24 data were used for Study 1100.1526. Safety endpoints for both trials included AEs, investigator-defined drug-related AEs, premature discontinuations due to AEs, serious adverse events (SAEs), rash and hepatic events, and laboratory abnormalities.

This NDA also contained safety data from four Phase 1 trials (1100.1484, 1100.1485, 1100.1517, and 1100.1489) conducted in adult subjects to characterize the bioavailability and PK of nevirapine XR. Three of these trials were single-dose studies conducted in healthy volunteers and the fourth was a multiple-dose study conducted in HIV-1 infected subjects. Since the treatment doses, durations and subject populations in these Phase 1 trials were considerably different from the Phase 3 program, safety data from these trials will be considered apart and summarized here.

Study 1100.1484 was a trial of nevirapine absorption in different segments of the intestinal tract. Twenty-seven healthy male volunteers were randomized and received at least 1 dose of nevirapine. The study drug was nevirapine in a capsule or suspension control; no nevirapine XR was used in this trial. The safety analysis included all 27 subjects; 4 of whom received one 50 mg dose, 8 received two 50 mg doses, and 15 received three 50 mg doses of nevirapine.

Study 1100.1485 was a bioavailability trial of 5 different NVP XR prototype formulations at 2 doses compared to 2 doses of NVP IR. This trial enrolled 204 healthy male volunteers, each of whom received 1 dose of nevirapine. The safety analysis included all 204 subjects, of whom 17 received 1 dose of 200 mg nevirapine IR, 85 received 1 dose of 300 mg nevirapine XR, and 102 received 1 dose of 400 mg nevirapine IR or XR.

Study 1100.1517 was a bioavailability trial to determine the PK of a 100 mg XR tablet (b) (4). This trial enrolled 96 healthy male volunteers, each of whom took nevirapine. The safety analysis included all 96 subjects, comprising 4 groups of 24 subjects. Each group received one of the following doses: 200 mg nevirapine (2 x nevirapine XR 100 mg) or 300 mg nevirapine (3 x nevirapine XR 100 mg) or 400 mg

nevirapine (1 x nevirapine XR 400 mg) or 200 mg nevirapine (1 x nevirapine IR 200 mg, Viramune®).

Study 1100.1489 was a bioavailability trial in HIV-1 infected subjects evaluating the bioavailability of 2 NVP XR prototype formulations at 2 doses. The PK results from this trial are summarized in Section 6.1.8 of this review. In this trial, 92 subjects received at least 1 dose of NVP XR and are included in the safety analysis. Exposure to study drug is as follows:

- 19 days of once-daily nevirapine XR were taken by:
  - 21 subjects who received nevirapine XR 300 mg [KCR 20%] (including 1 subject who received a total of 26 days (19+7) due to a 7-day hospitalization during which the subject continued to take additional study drug)
  - 21 subjects who received nevirapine XR 300 mg [KCR 25%]
  - 23 subjects who received nevirapine XR 400 mg [KCR 20%]
  - 24 subjects who received nevirapine XR 400 mg [KCR 25%];
- 18 days were taken by 2 subjects (both subjects were receiving nevirapine XR 300 mg [KCR 20%] and both missed a study visit)
- 7 days of nevirapine XR 400 mg [KCR 20%] were taken by 1 subject received who voluntarily withdrew early from the trial.

Across the three single dose PK studies in 327 healthy volunteers (Studies 1100.1484, 1100.1485, and 1100.1517), no new or unexpected adverse events were observed. There was a single unrelated SAE, no deaths, and two study discontinuations due to an AE. Investigator-defined drug-related AEs were generally mild. There was an AE of mild rash reported in a recipient of nevirapine IR. In the multiple-dose PK study (Study 1100.1489), among 24 HIV-1-infected subjects treated for 3 weeks, there was a single unrelated SAE, no deaths, no severe or life-threatening AEs, and no AE that led to study discontinuation.

### 7.1.2 Categorization of Adverse Events

In the NVP XR clinical trials, AEs were coded according to MedDRA (Version 12.1) preferred terms. AEs that were noted as drug-related were those that were considered by the investigator to be related to study drugs. Adverse event intensity was graded based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Dec. 2004). AEs were tabulated for both Phase 3 trials for all occurrences, by intensity, for all moderate or severe (DAIDS Grade  $\geq 2$ ) occurrences, and for drug-related moderate or severe occurrences.

Adverse drug reactions (ADRs) reflect AEs which have been causally related to the use of nevirapine by the investigator or sponsor. The applicant maintains a list of ADRs as part of the company core data sheet (CCDS) for nevirapine. The AEs occurring in Study

1100.1486 were reviewed internally by the medical project team and global pharmacovigilance team to identify those preferred terms using MedDRA version 12.1 that corresponded to the initial list in the CCDS. An updated revised list of ADRs was then generated. There were minor differences in the ADR list and preferred terms used, primarily due to updating of MedDRA.

In categorizing AEs, particularly rash and hepatotoxicity events, the applicant tended to split terms so that the overall rates of certain AEs differed from this reviewer's analysis. For example, cases of Stevens-Johnson syndrome were counted separately from cases of rash and cases of hepatic failure were counted apart from case of hepatitis. In reporting the major safety findings in this review, this reviewer has listed AEs by MedDRA system organ class (SOC) and preferred term (PT) to minimize the effect of such splitting.

### 7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Given the different study populations and trial designs of Studies 1100.1486 and 1100.1526, data from the two trials were generally not pooled. In one instance, for a broad overview of common adverse events observed with NVP XR, the safety data were pooled and analyzed but the exercise did not provide any new useful information regarding the safety profile of NVP XR.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1219 study participants in four Phase 1 and two Phase 3 trials received at least one dose of nevirapine XR: 892 were HIV-1-infected subjects and 327 were healthy volunteers. In the Phase 3 trials, 295 treatment-experienced subjects received at least 24 weeks, and 505 treatment-naïve subjects received at least 48 weeks of nevirapine XR with the final formulation and intended marketed dose.

### 7.2.2 Explorations for Dose Response

Study 1100.1489 was a bioavailability trial that explored two doses of NVP XR (300 mg and 400 mg) in treatment-experienced HIV-1 infected subjects already on a nevirapine IR-based ARV regimen. The PK results of that trial showed the 300 mg dose of NVP XR resulted in  $C_{min}$  levels below the target level considered necessary for efficacy ( $C_{min,ss} \approx$

3000 ng/mL). The 400 mg dose, on the other hand, resulted in  $C_{min}$  levels that were closer to target, albeit still lower than concentrations achieved with NVP IR. Consequently, the 400 mg dose of NVP XR was selected for evaluation in the Phase 3 trials. (See Section 6.1.8 for further discussion of Study 1100.1489 PK results.) No other dose level was explored in these trials.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed or required.

### 7.2.4 Routine Clinical Testing

The routine clinical testing performed during the two Phase 3 clinical trials was appropriate for the disease and study population under evaluation.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance, and drug-drug interactions of nevirapine are well described in the current USPI for Viramune®.

Both *in vitro* dissolution studies and *in vivo* absorption, bioavailability and PK evaluations (in humans) were conducted as part of the development program for the nevirapine XR tablet. Details of these assessments can be found in Sections 4.4 (Clinical Pharmacology) and Sections 5.3 and 7.1.1 (Clinical Trials). Further discussion can also be found in the Clinical Pharmacology review by Dr. Vikram Arya.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No new adverse events were reported in the course of these clinical trials that would warrant evaluation for potential adverse events for similar drugs in the NNRTI drug class.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were a total of 10 deaths in Study 1100.1486 from inception to the Week 48 database lock. Four deaths occurred during screening and 6 deaths occurred after

initiation of randomized treatment (IR 5, XR 1). No deaths occurred during the lead-in phase. None of the 6 deaths in the randomized phase were considered drug-related. Of the 6 deaths in the randomized phase, 4 occurred while subject was receiving study drug. The other 2 subjects (Subjects 16037 and 16314) had stopped treatment before their deaths.

Subject 16037 (NVP IR) died on Day 138 due to tuberculous meningitis, which had been diagnosed on Day 17 along with pulmonary tuberculosis. His compliance with both antiretrovirals and antituberculosis therapy was poor and he was discontinued from the trial on Day 89 due to non-compliance. He was hospitalized that same day for tuberculous meningitis and died approximately 2 months later. The cause of death was disseminated tuberculosis. No autopsy was performed.

Subject 16314 (NVP IR) discontinued study drug on Day 153 due to worsening pulmonary hypertension, which was diagnosed at screening. She was hospitalized that same day and died acutely on Day 171 of respiratory failure.

Two subjects died at home, while on study drug, of cardiovascular causes. Subject 10529 (NVP IR) was a 29-year-old male with history of moderate hypertension who suffered a myocardial infarction (MI) which led to his death at home on Day 440. The MI was confirmed by autopsy. Subject 14349 (NVP XR) was a 64-year-old male with history of arteriosclerosis and hypertension. This subject died at home on Day 158. An autopsy was not performed. The cause of death was reported as hypertension and atherosclerotic disease on the death certificate. The 6 deaths in Study 1100.1486 are listed in Table 15 by time in trial. Causes of death are listed by MedDRA preferred term (PT).

**Table 15: Summary of Deaths (Study 1100.1486)**

Subject ID	Age/Sex	Treatment	Cause of death (MedDRA PT)	Study Day	Region
18677	40 male	NVP IR	Pneumonia	53	Africa
			Encephalopathy		
16577	36 male	NVP IR	Thermal burn	97	Africa
			Wound sepsis		
16037	43 male	NVP IR	Meningitis tuberculous/ disseminated tuberculosis	138	Europe
14349	64 male	NVP XR	Arteriosclerosis	158	North America
			Hypertension		
16314	23 female	NVP IR	Respiratory alkalosis	171	Africa
10529	29 male	NVP IR	Myocardial infarction	440	Europe

Source: Integrated Safety Summary

No deaths occurred in Study 1100.1526.

### 7.3.2 Nonfatal Serious Adverse Events

#### Study 1100.1486

Of the 1068 subjects who entered the lead-in phase, 20 (2%) subjects experienced 19 serious adverse events (SAEs) during lead in treatment with NVP IR 200 mg QD. For 14 of these subjects, the SAE was considered treatment-related. The most frequently reported SAEs by system organ class (SOC) were Skin and Subcutaneous Tissue SOC and Infections and Infestations SOC, both with 7 (1%) subjects each. The most frequently reported SAE by preferred term (PT) was rash, found in 5 (<1%) subjects. An additional 2 subjects developed Stevens-Johnson syndrome (SJS). Two subjects experienced pyrexia (1 with rash, 1 with arthralgia) and 2 additional subjects experienced hypersensitivity reactions. The SAEs of rash, SJS, pyrexia and hypersensitivity were all considered study drug-related. The 10 subjects with these SAEs all discontinued from the trial and were not randomized. Another subject experienced Grade 4 neutropenia (not drug related) and also discontinued. Of the 7 subjects with infectious SAEs, 6 continued in the trial and were randomized and 1 subject with meningitis tuberculosis discontinued (Subject 16235 in South Africa).

Of the 1011 subjects randomized and treated in this trial, 112 (11%) subjects experienced 133 SAEs. The proportion of subjects with SAEs was comparable between the two treatment groups (IR 54 [11%], XR 58 [12%]). The SOC with the highest rates of SAEs was Infections and infestations (41 [4%]), followed by the Psychiatric disorders SOC and Injury, poisoning, procedural complications SOC with 12 subjects (1%) each. Most of the events in the two latter categories involved depression or accidents, respectively. The most frequently reported SAEs by PT were pneumonia, depression and Kaposi's sarcoma, each with 5 (0.5%) subjects overall. The number of subjects with SAEs in the Hepatobiliary disorders and Skin and subcutaneous tissue disorders SOCs was small (9 and 7, respectively) but balanced between the two treatment groups. Of note, 3 (1%) subjects in the NVP IR group experienced SJS; all 3 had event onset within 15 days of starting randomized study drug (Day 1, 8 and 15). All 3 subjects recovered with discontinuation of study drug.

The more frequently reported SAEs and SAEs of special interest (e.g., hepatitis and rash) are listed in Table 16 by SOC and PT.

**Table 16: Serious Adverse Events during Randomized Phase (Study 1100.1486)**

Serious adverse events (by SOC/PT) <sup>a, b</sup>	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Number with any SAEs	54 (11)	58 (12)	112 (11)
Infections and infestations	17 (3)	24 (5)	41 (4)
Pneumonia	3 (1)	2 (<1)	5 (1)
Psychiatric disorders	7 (1)	5 (1)	12 (1)
Depression	3 (1)	2 (<1)	5 (1)
Injury, poisoning, procedural complications	8 (2)	4 (10)	12 (1)
Neoplasms	4 (1)	6 (1)	10 (1)
Kaposi's sarcoma	3 (1)	2 (<1)	5 (1)
Gastrointestinal disorders	5 (1)	5 (1)	10 (1)
Hepatobiliary disorders	5 (1)	4 (1)	9 (1)
Cholelithiasis	1 (<1)	1 (<1)	2 (<1)
Hepatotoxicity	2 (<1)	0	2 (<1)
Biliary colic	1 (<1)	0	1 (<1)
Cytolic hepatitis	0	1 (<1)	1 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Hepatic necrosis	0	1 (<1)	1 (<1)
Hepatitis	1 (<1)	0	1 (<1)
Hepatitis acute	1 (<1)	0	1 (<1)
Hepatitis toxic	0	1 (<1)	1 (<1)
Investigations	2 (<1)	2 (<1)	4 (<1)
ALT increased <sup>c</sup>	1 (<1)	2 (<1)	3 (<1)
AST increase <sup>c</sup>	1 (<1)	2 (<1)	3 (<1)
Bilirubin increased	0	1 (<1)	1 (<1)
GGT increased <sup>c</sup>	0	1 (<1)	1 (<1)
Transaminases increased	1 (<1)	0	1 (<1)
Skin and soft tissue disorders	4 (1)	3 (1)	7 (1)
Stevens-Johnson syndrome	3 (1)	0	3 (<1)
Rash	1 (<1)	1 (<1)	2 (<1)
Drug rash with eosinophilia	0	1 (<1)	1 (<1)
Erythema multiforme	0	1 (<1)	1 (<1)

<sup>a</sup> SOC=system organ class, PT=preferred term

<sup>b</sup> Subjects may have more than one PT event within each SOC

<sup>c</sup> ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyltransferase

Source: AE dataset

### Study 1100.1526

Of the 443 randomized and treated subjects in Study 1100.1526, 21 (5%) subjects experienced 26 SAEs. SAEs occurred twice as frequently in the NVP XR group (17 [6%]) than in the NVP IR group (4 [3%]); however, none of the SAEs were considered treatment-related and all subjects continued study drug. Given the small number of subjects with SAEs, there was no discernable pattern regarding the specific types of events. The Infections and infestations SOC had the most subjects with SAEs (7 subjects), followed by the Injury, poisoning and procedural SOC (5 subjects). There were no reported SAEs consistent with rash or hepatitis. The most frequently reported SAE by PT was bronchitis with 2 (1%) subjects, both in the NVP XR group.

### 7.3.3 Dropouts and/or Discontinuations

#### Study 1100.1486

As noted in Section 6.1.3 (Subject Disposition), 55 (5%) of 1068 subjects discontinued Study 1100.1486 during the lead-in phase. Subjects in this group discontinued nevirapine at various points in time during the 2 week lead-in phase. Most subjects received greater than 1 week but less than 3 weeks of lead-in phase dosing. Seven patients exceeded the maximum 4-week dosing period for the lead-in phase due to a temporary shortage of blinded medication kits, necessitating a prolongation of the lead-in phase until such kits were available and randomization could occur. Five of these 7 patients remained on lead-in dose for only an extra day while the other 2 did so for a little over a week.

Of the 55 subjects who discontinued therapy during the lead-in phase, 45 (4% of lead-in population) stopped study drug treatment due to an AE. Eight of these subjects had reintroduction of nevirapine and proceeded onto randomization. One subject (Subject 10131) reported a Grade 2 headache during the lead-in phase but continued study drug; this subject, however, did not go onto randomization and the reason cited was AE. Among the 37 (3%) subjects who discontinued study drug completely due to AEs, the more significant AEs were rash (n=28, including 2 cases of SJS), hypersensitivity reactions (3), hepatitis (1), and increased ALT (1). Two additional subjects who reported rash during the lead-in had nevirapine reintroduced, but neither continued onto the randomized phase despite this.

During the randomized phase of the trial, 77 (8%) of 1011 treated subjects discontinued study drug due to AEs (IR 45 [9%], XR 32 [6%]). The most common AEs leading to study drug discontinuation were rash (including SJS), increased transaminases, hepatotoxicity, and nausea. The NVP IR group tended to have more AEs in each of the leading SOC categories compared to the NVP XR group, but the differences in rates

were small. However, there were 3 cases of SJS in the NVP IR group compared to 0 in the XR group (the 3 cases are discussed in Section 7.3.2, SAEs). No relationship was detected between trough level and frequency of discontinuation of study drug due to an AE when either the steady state trough level or the Week 2 trough level was considered. Table 17 lists the leading AEs that led to study drug discontinuation during the randomization phase by MedDRA SOC and PT.

**Table 17: Adverse Events leading to Study Drug Discontinuation during Randomized Phase (Study 1100.1486)**

Adverse events leading to discontinuation (by SOC/PT) <sup>a</sup>	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Number with AEs	45 (9)	32 (6)	77 (8)
Skin and subcutaneous tissue disorders	18 (4)	11 (2)	29 (3)
Rash	12 (2)	9 (2)	21 (2)
Stevens-Johnson syndrome	3 (1)	0	3 (<1)
Drug rash with eosinophilia	0	1(<1)	1(<1)
Investigations	16 (3)	8 (2)	24 (2)
Transaminases increased	3 (1)	3 (1)	6 (1)
ALT increased	4 (1)	1(<1)	5 (1)
GGT increased	2 (<1)	2 (<1)	4 (<1)
AST increased	2 (<1)	1 (<1)	3 (<1)
Hepatic enzyme increased	1 (<1)	1 (<1)	2 (<1)
Hepatobiliary disorders	14 (3)	9 (2)	23 (2)
Hepatitis	5 (1)	3 (1)	8 (1)
Hepatotoxicity	4 (1)	2 (<1)	6 (1)
Hepatitis acute	2 (<1)	1 (<1)	3 (<1)
Hepatitis toxic	1 (<1)	1(<1)	2 (<1)
Gastrointestinal disorders	5 (1)	2 (<1)	7 (1)
Nausea	3 (1)	2 (<1)	5 (1)
Infections and infestations	4 (1)	3 (1)	7 (1)
General disorders <sup>b</sup>	3 (1)	2 (<1)	5 (1)
Vascular disorders	1 (<1)	2 (<1)	3 (<1)
Musculoskeletal and connective tissue disorders	0	2 (<1)	2 (<1)
Neoplasms	1 (<1)	1 (<1)	2 (<1)
Kaposi's sarcoma	1 (<1)	0	1 (<1)
Non-Hodgkin's lymphoma	0	1 (<1)	1 (<1)
Nervous system disorders	2 (<1)	0	2 (<1)

Immune disorders	1 (<1)	0	1 (<1)
Drug hypersensitivity	1 (<1)	0	1 (<1)

<sup>a</sup> SOC=system organ class; PT=preferred term

<sup>b</sup> General disorders include malaise, pyrexia, and fatigue

Source: AE dataset

### Study 1100.1526

In Study 100.1526, three subjects discontinued treatment due to AE; all 3 (1%) were in the NVP XR group. Subject 3405 reported 11 AEs within 1-3 days of switching to NVP XR. The AEs covered a wide spectrum of symptoms, including anxiety, smell alteration, headache, lethargy, dry mouth, indigestion, and tachycardia. None of these AEs were considered drug-related by the investigator. Subject 4038 discontinued treatment on Day 1 due to a Grade 2 rash that was considered drug-related and Subject 4163 discontinued treatment on Day 1 due to Grade 1 nausea and lightheadedness that were also considered drug-related.

## 7.3.4 Significant Adverse Events

### Study 100.1486

During the lead-in phase, 210 (20%) of 1068 subjects experienced investigator-defined drug-related AEs, of any intensity. The most common drug-related AEs were rash (7%), nausea (4%), headache (3%) and fatigue (2%). Drug-related AEs classified as DAIDS Grade  $\geq 2$  included rash (3%), headache (1%), pyrexia (1%), nausea (1%) and fatigue (1%). Severe (Grade 3) rash was experienced in 13 (1%) subjects, including one case of SJS (Subject 18780). Another subject (13972) experienced SJS that was DAIDS Grade 2. Both subjects with SJS discontinued study drug. There was 1 case of a Grade 4 drug-related AE in the lead-in phase (elevated transaminases); this subject also discontinued study drug.

During the randomized phase, 223 (22%) of 1011 subjects experienced investigator-defined drug-related AEs, of any severity. The most commonly reported drug-related AEs were rash and liver function test abnormalities. Rash was reported in 27 (5%) subjects in the NVP IR group and 30 (6%) subjects in the NVP XR group. In general, rash occurred early after randomization. Mean time of onset for rash was 12.6 days (median 10, min 1, max 65) in the NVP IR group and 20 days (median 12, min 1, max 148) in the NVP XR group. Liver function test abnormalities were reported in 4% of subjects in each treatment group (IR 22, XR 20). Nausea and headache were reported more frequently in the NVP IR group. Overall, however, the rates of drug-related AEs were fairly well balanced between the two arms.

A total of 120 (12%) of 1011 randomized subjects had AEs that were of at least moderate intensity, i.e. DAIDS Grade  $\geq 2$  (IR 66 [13%], XR 54 [11%]). Rash, increased transaminases and hepatotoxicity were the leading drug-related DAIDS Grade  $\geq 2$  AEs. Again, the proportion of subjects with moderate to severe drug-related AEs was comparable between the two treatment groups. Grade  $\geq 2$  drug-related rash events (using multiple preferred terms for rash) was reported in 3% of subjects in each treatment arm. Stevens-Johnson syndrome, however, was reported solely in the NVP IR group (3 cases, discussed in Section 7.3.2). Other Grade  $\geq 2$  drug-related AEs reported in the NVP IR group but not the NVP XR group included pyrexia, diarrhea, fatigue, viral load increase and insomnia. Grade  $\geq 2$  drug-related hepatic events also tended to occur more frequently in the NVP IR group. Table 18 summarizes drug-related AEs, Grades 2-4, by SOC or PT.

**Table 18: Drug-related Moderate or Severe (DAIDS Grade  $\geq 2$ ) Adverse Events during Randomized Phase (Study 1100.1486)**

DAIDS Grade 2-4 adverse events (by SOC/ADR/PT) <sup>a</sup>	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Number with AEs	66 (13)	54 (11)	120 (12)
Skin and subcutaneous tissue disorders	20 (4)	21(4)	41(4)
Rash	15 (3)	17 (3)	32 (3)
Rash	12 (2)	16 (3)	28 (3)
Rash maculo-papular	2 (<1)	0	2 (<1)
Erythema nodosum	1 (<1)	0	1 (<1)
Rash erythematous	1 (<1)	0	1 (<1)
Rash papular	1 (<1)	0	1 (<1)
Skin reaction	0	1 (<1)	1 (<1)
Stevens-Johnson syndrome	3 (1)	0	3 (<1)
Dermatitis allergic	0	1 (<1)	1 (<1)
DRESS syndrome <sup>b</sup>	0	1 (<1)	1 (<1)
Investigations	29 (6)	24 (5)	53 (5)
Liver Function Test Abnormal	18 (4)	15 (3)	33 (3)
Alanine aminotransferase increased	6 (1)	6 (1)	12 (1)
Transaminases increased	6 (1)	5 (1)	11 (1)
Aspartate aminotransferase increased	3 (1)	5 (1)	8 (1)
Gamma-glutamyltransferase increased	3 (1)	2 (<1)	5 (1)
Liver function test abnormal	3 (1)	0	3 (<1)
Hepatic enzyme increase	2 (<1)	1 (<1)	3 (<1)
Hypertransaminasemia	1 (<1)	0	1 (<1)
Hepatobiliary disorders	18 (4)	9 (2)	27 (3)

Hepatitis	17 (3)	9 (2)	26 (3)
Hepatitis	6 (1)	4 (1)	10 (1)
Hepatotoxicity	6 (1)	2 (<1)	8 (1)
Hepatitis acute	2 (<1)	1 (<1)	3 (<1)
Hepatitis toxic	1 (<1)	1 (<1)	2 (<1)
Liver disorder	2 (<1)	0	2 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Jaundice	1 (<1)	0	1 (<1)
Gastrointestinal disorders	13 (3)	4 (1)	17 (2)
Nausea	5 (1)	1 (<1)	6 (1)
Metabolism and nutrition disorders	2 (<1)	4 (1)	6 (1)
Musculoskeletal and connective tissue disorders	3 (1)	2 (<1)	5 (1)
Nervous system disorders	4 (1)	5 (1)	9 (1)
Headache	3 (1)	3 (1)	6 (1)

<sup>a</sup> SOC=system organ class; ADR=adverse drug reaction (BI term); PT=preferred term

<sup>b</sup> DRESS=drug rash with eosinophilia and systemic systems

Source: AE dataset

Of the 1011 randomized subjects, 48 (5%) reported severe (DAIDS Grade 3) drug-related AEs (IR 28 [6%], XR 20 [4%]). The majority of these events involved abnormal liver function tests or hepatotoxicity and occurred slightly more frequently in the NVP IR arm, but the overall rates were comparable between the two groups. Severe drug-related rash was reported in 4 (1%) subjects in the NVP IR group and 2 (0.4%) subjects in the NVP XR group. Two additional subjects in the NVP IR group experienced Grade 3 Stevens-Johnson syndrome.

Twelve (12) Grade 4 drug-related AEs were reported among 14 subjects, mostly in the NVP IR group (IR 9 [2%], XR 5 [1%]). The majority of these events consisted of abnormal liver function tests or hepatotoxicity. One event of Grade 4 SJS and one event of Grade 4 acute hepatitis (1 subject each) in the NVP IR group were considered serious and required hospitalization.

Thirty-one (3%) subjects had new AIDS events (IR 19 [4%], XR 12 [2%]) during the course of the trial. The majority of these events were infectious-related or neoplastic (Kaposi's sarcoma, lymphoma).

### Study 1100.1526

A total of 38 (9%) of 443 subjects experienced investigator-defined drug-related AEs of any intensity. The vast majority of these subjects were in the NVP XR group (IR 3 [2%], XR 35 [12%]). The leading drug-related AEs were fatigue, nausea, and diarrhea. These AEs occurred at a rate of 1% of the total study population, exclusively in the NVP XR treatment arm, and were all of DAIDS Grade 1 intensity (Table 19). Drug-related rash (1

subject) and abnormal liver function tests (2 subjects) were also reported in the NVP XR group.

**Table 19: Drug-related Adverse Events of Any Intensity in  $\geq$  1% of Subjects in Any Treatment Group (Study 1100.1526)**

Adverse event	DAIDS Toxicity	Number of subjects (%)		
		NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Any AE		3 (2)	35 (12)	38 (9)
Fatigue	Grade 1	0	5 (2)	5 (1)
Nausea	Grade 1	0	4 (1)	4 (1)
Diarrhea	Grade 1	0	3 (1)	3 (1)
Hypertension	Grade 1	1 (1)	2 (1)	3 (1)
Dizziness	Grade 1	0	2 (1)	2 (<1)
Dysgeusia	Grade 1	0	2 (1)	2 (<1)
Medication residue	Grade 1	0	2 (1)	2 (<1)
Pruritus	Grade 1	0	2 (1)	2 (<1)

Source: AE dataset

Drug-related AEs of at least moderate severity (DAIDS Grade  $\geq$  2) were limited in this trial and consisted predominantly of laboratory test abnormalities. Eleven drug-related Grade  $\geq$  2 AEs were reported among 10 subjects (IR 2 [1%], XR 8 [3%]). These included nausea, pancreatic insufficiency, ALT/AST increase, impaired glucose tolerance, insomnia, macular rash, and hypertensive crisis; each AE occurred in 1 (<1%) subject in the NVP XR arm. One subject in the NVP XR arm had a Grade 3 ALT increase. One subject in the NVP IR arm (Subject 4258) had Grade 2 lipase increase and Grade 3 amylase increase, without reported symptoms of pancreatitis. Another subject in the NVP IR arm had Grade 3 blood triglycerides increase. No Grade 4 drug-related AEs were reported in this trial.

A single subject (Subject 4554 in the NVP XR group) experienced progression of an AIDS-related illness. This subject had a previous history of Kaposi's sarcoma in January 1986, treated with excision and radiation at the time. In [REDACTED] (b) (6) approximately 16 days after randomization in Study 1100.1526, a punch biopsy of the left foot revealed recurrence of Kaposi's sarcoma.

### 7.3.5 Submission Specific Primary Safety Concerns

The primary safety concerns associated with nevirapine therapy are rash and hepatotoxicity. These two safety issues are discussed here within the context of the Phase 3 trials for NVP XR.

➤ Rash

An in-depth analysis of rash events was conducted as part of this review. In analyzing the AE datasets submitted by the applicant, it was noted that some rash events were coded multiple times using different PTs for the same event or different DAIDS grades for the same event over time. In these instances, one PT and the most severe DAIDS grade was selected for each individual subject if the rash represented a single event. For example, in Study 1100.1486, Subject 17612 had a rash event that was entered 4 times using different PTs for the same event; in this case, one PT was selected and the subject was counted once. Subject 17677 had a Grade 2 rash that evolved to Grade 3 SJS within 12 days; in this case, only the SJS event was counted for the analysis.

In Study 1100.1486, there was no significant difference in the frequency or severity of rash events between the NVP IR and NVP XR treatment groups (odds ratio [OR] = 1). Most rash events occurred early in treatment, either during the lead-in phase or shortly after randomization (mean time: 13 days NVP IR, 20 days NVP XR). Severe or life-threatening rash (Grade 3/4) occurred twice as frequently in the NVP IR arm than in the NVP XR arm (IR 7 [1.4%], XR 3 [0.6%]), but the total numbers were too small to draw any significant conclusions. Five cases of SJS were reported, 2 during the lead-in phase and 3 shortly after randomization (all in the NVP IR group). All SJS events occurred within 30 days of starting treatment. Per the AE datasets, one of the SJS cases was Grade 4, three were Grade 3, and one case during the lead-in phase was Grade 2. However, per the applicant's integrated summary of safety, the latter case was judged to be Grade 4. Given the nature of SJS, this reviewer concurs that the case was likelier to have been Grade 4 in severity. Table 20 lists the frequency of rash events by DAIDS grade severity, as reported in the AE datasets.

**Table 20: Rash Events by DAIDS Grade Severity (Study 1100.1486)**

DAIDS Grade	Number of subjects (%)				
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)	Lead-in Phase (N=1068)	Lead-in, Not Randomized (N=55)
1	13 (3)	13 (3)	26 (3)	35 (3)	4 (7)
2	10 (2)	16 (3)	26 (3)	26 (2)	17 (30)
3	6 (1)	2 (<1)	8 (1)	13 (1)	13 (24)
4	1 (<1)	1 (<1)	2 (<1)	0	0
Total	30 (6)	32 (6)	62 (6)	74 (7)	34 (62)

Source: AE dataset

Per the protocol for Study 1100.1486, a special rash CRF was to be completed for subjects who experienced a potentially drug-related rash during the course of the trial.

This additional CRF, however, was inconsistently completed by the investigators. Moreover, discrepancies were noted between the AE and rash CRFs regarding severity or causality of events. Therefore, adjudication of rash events (blinded to treatment) was conducted by the applicant, using a defined set of rules, to derive a new dataset of rash events for analysis. The applicant's analysis of adjudicated rash events yielded a higher total number of events than reported in Table 20, particularly for Grade 1 events. In addition, as previously noted, the applicant identified a Grade 4 SJS event occurring in the lead-in phase (subject not randomized), that was coded as Grade 2 in the AE dataset. The overall conclusions reached by the applicant regarding the relative frequencies of rash events, however, are consistent with this reviewer's analysis.

Further discussion of rash events in Study 1100.1486 can be found in Section 7.5.3 (Drug-Demographic Interactions) and Section 7.5.4 (Drug-Disease Interactions).

In Study 1100.1526, drug-related rashes occurred in only 3 (1%) of 443 subjects. All 3 subjects were male and all 3 were in the NVP XR group (3/295 [1%]). Two of these events (macular rash and allergic urticaria) were Grade 1 and one event was Grade 2 (macular rash). The latter event occurred on Day 1 of the switch and led to treatment discontinuation (Subject 4038). In conclusion, rash was not a significant safety finding in the nevirapine IR to XR switch study.

➤ Hepatotoxicity

The AE datasets identified 28 (3%) subjects with hepatic events (any grade) during the randomization phase of Study 1100.1486; this figure does not account for cases of asymptomatic transaminase elevations if such events were not coded as an AE. The majority of these events occurred in the NVP IR group (IR 19 [4%], XR 9 [2%]). The NVP IR group also had a greater proportion of DAIDS Grade 3 or 4 events (IR 13 [3%], XR 7 [1%]). Mean time to onset of hepatic event was roughly 6 weeks for NVP IR and 8 weeks for NVP XR.

Per the protocol for 1100.1486 investigators were also instructed to complete a hepatic CRF page for all subjects who developed clinical hepatitis or DAIDS Grade 3 or 4 transaminase elevation not attributable to an infectious agent while on study drug. The hepatic CRFs identified 73 (7%) subjects with a hepatic event in the randomized phase (n=1011), of whom 35 were identified as symptomatic. Following an internal review of the hepatic CRF data and supporting AE and laboratory data, 74 (7%) subjects were identified with a hepatic event during the randomized phase, 22 (2%) of whom were symptomatic. The most frequently occurring symptoms associated with hepatic events were anorexia, jaundice and vomiting. During the lead-in phase, only 5 (<1%) of 1068 subjects experienced a hepatic event, 3 of whom did not go on to randomization (all 3 subjects had a hypersensitivity reaction). There were no reports of asymptomatic transaminase elevations during the lead-in phase.

Of the 74 subjects in the adjudicated dataset who had hepatic events during the randomized phase, 47 (5%) discontinued from the trial, including 20 of 22 subjects with symptomatic events. One of these 20 subjects was a 23-year old male (Subject 11084) who experienced Grade 3 hepatic failure approximately 9 days after randomization while on NVP XR. He required hospitalization and discontinued nevirapine; the event resolved a month later. The 2 symptomatic subjects that remained in the trial had events that were not considered drug-related by the investigator and both recovered with additional therapy.

As was observed with the AE dataset, in the adjudicated hepatic event dataset, subjects in the NVP IR group were more likely to have a hepatic event than subjects in the NVP XR group (OR = 1.71). This held true for symptomatic events as well. There were greater total numbers and frequencies of subjects in the NVP IR group that either developed a hepatic event (IR 46 [9%], XR 27 [5%]), exhibited symptoms of hepatitis (IR 12 [2%], XR 8 [8%]), exhibited non-specific symptoms which could be associated with a hepatic event (IR 20 [4%], XR 10 [2%]) or had asymptomatic Grade 3 or 4 transaminase elevation (IR 24 [5%], XR 13 [3%]).

Further discussion of hepatic events in Study 1100.1486 can be found in Section 7.5.3 (Drug-Demographic Interactions) and Section 7.5.4 (Drug-Disease Interactions).

In Study 1100.1526, no hepatic events were attributed to study drug. Of note, 11 subjects had evidence of either acute or chronic hepatitis B or C infection at enrollment, but none developed clinical hepatic events or significant laboratory abnormalities during the course of the trial. As with rash, hepatotoxicity was not a major safety concern in this supportive switch trial.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

#### **Study 100.1486**

During the lead-in phase, 465 (44%) of 1068 subjects experienced AEs of any causality. The most commonly reported AEs were rash (7%), nausea (6%), headache (5%), fatigue (4%), diarrhea (3%) and pyrexia (2%). Among the 55 subjects not randomized, rates for some of these AEs were greater: rash (56%), pyrexia (26%), headache (11%), fatigue (9%), nausea (7%), and vomiting (6%).

During the randomized phase of the trial, 895 (89%) of 1011 subjects experienced AEs of any causality; the rates were comparable between the two arms: IR 452 (89%), XR 443 (88%). Table 21 lists the more commonly reported AEs regardless of causality.

**Table 21: Adverse Events in ≥ 3% of Subjects Overall during Randomized Phase (Study 1100.1486)**

Adverse events	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Any adverse event	452 (89%)	443 (88%)	895 (89%)
Nasopharyngitis	83 (16)	90 (18)	173 (17)
Diarrhea	62 (12)	62 (12)	124 (12)
Upper respiratory tract infection	54 (11)	51(10)	105 (10)
Rash	48 (9)	53 (10)	101 (10)
Headache	59 (12)	39 (8)	98 (10)
Nausea	50 (10)	30 (6)	80 (8)
Bronchitis	31 (6)	36 (7)	67 (7)
Cough	33 (7)	23 (5)	56 (6)
Vomiting	31 (6)	23 (5)	54 (5)
Gastroenteritis	24 (5)	25 (5)	49 (5)
Back pain	23 (5)	25 (5)	48 (5)
Fatigue	24 (5)	24 (5)	48 (5)
Influenza	25 (5)	20 (4)	45 (4)
Arthralgia	25 (5)	19 (4)	44 (4)
Hypertension	23 (5)	21 (4)	44 (4)
Abdominal pain	22 (4)	18 (4)	40 (4)
Depression	23 (5)	15 (3)	38 (4)
Insomnia	22 (4)	15 (3)	37 (4)
Pyrexia	21 (4)	14 (3)	35 (3)
Anogenital warts	15 (3)	19 (4)	34 (3)
Myalgia	16 (3)	17 (3)	33 (3)
Oropharyngeal pain	14 (3)	19 (4)	33 (3)
Sinusitis	17 (3)	16 (3)	33 (3)
Pharyngitis	16 (3)	16 (3)	32 (3)
Herpes zoster	15 (3)	16 (3)	31 (3)
Folliculitis	15 (3)	15 (3)	30 (3)
Anxiety	16 (3)	12 (2)	28 (3)
Respiratory tract infection	13 (3)	14 (3)	27 (3)
Urinary tract infection	10 (2)	17 (3)	27 (3)
Eczema	10 (2)	16 (3)	26 (3)

Source: AE dataset

Study 1100.1526

In this trial, 312 (70%) subjects reported an AE of any causality, with higher rates for subjects who switched to the NVP XR than for those who remained on their previous NVP IR therapy (IR 89 [60%], XR 223 [76%]). The most commonly reported AEs are listed in Table 22.

**Table 22: Adverse Events Occurring in ≥ 2 % of Subjects Overall (Study 1100.1526)**

Adverse events	Number of subjects (%)		
	NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Any AE	89 (60)	223 (76)	312 (70)
Nasopharyngitis	14 (9)	27 (9)	41 (9)
Diarrhea	5 (3)	26 (9)	31 (7)
Bronchitis	9 (6)	13 (4)	22 (5)
Fatigue	4 (3)	15 (5)	19 (4)
Sinusitis	8 (5)	11 (4)	19 (4)
Upper respiratory tract infection	2 (1)	17 (6)	19 (4)
Back pain	6 (4)	12 (4)	18 (4)
Hypertension	7 (5)	11 (4)	18 (4)
Cough	5 (3)	11 (4)	16 (4)
Headache	3 (2)	13 (4)	16 (4)
Arthralgia	4 (3)	9 (3)	13 (3)
Insomnia	2 (1)	9 (3)	11 (2)
Nausea	1 (1)	8 (3)	9 (2)
Sleep disorder	2 (1)	7 (2)	9 (2)
Syphilis	2 (1)	7 (2)	9 (2)
Depression	1 (1)	7 (2)	8 (2)

Source: AE dataset

Adverse events reported more frequently in the NVP XR group than in the NVP IR group tended to fall into 6 SOC categories: Gastrointestinal disorders, Psychiatric disorders, Nervous system disorders, Skin and subcutaneous tissue disorders, General disorders and administrative site conditions, and Injury, poisoning, and procedural complications. Within these SOCs, individual PTs occurred at a frequency < 2%. The vast majority of AEs within these SOCs were DAIDS Grade 1 (mild). DAIDS Grade ≥ 2 AEs were comparable between the two treatment groups, as demonstrated in Table 23.

**Table 23: Adverse Events by Leading SOC and DAIDS Grade (Study 1100.1526)**

SOC <sup>a</sup>	Number of subjects (%)							
	NVP IR 200 mg BID (N=148)				NVP XR 400 mg QD (N=295)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal disorders	7 (5)	4 (3)	0	0	82 (28)	13 (4)	0	0
General disorders and administration site conditions	8 (5)	1 (1)	0	0	35 (11)	3 (1)	3 (1)	0
Nervous system disorders	6 (4)	4 (3)	0	0	27 (9)	8 (3)	2 (1)	0
Skin and subcutaneous tissue disorders	7 (5)	0	0	0	36 (12)	4 (1)	0	0
Psychiatric disorders	7 (5)	1 (1)	0	0	26 (9)	7 (2)	0	1 (<1)
Injury, poisoning and procedural complications	3 (2)	2 (1)	0	0	23 (8)	10 (3)	1 (<1)	0

<sup>a</sup> SOC=system organ class

Source: AE dataset

### Pooled analysis

Pooling of the data from Studies 1100.1486 and 1100.1526, while not wholly suitable given the different study designs and populations, reveals that the patterns of AEs noted within each trial persist when the data are pooled. Rash, however, which was not a major finding in Study 1100.1526, became more prominent when the studies are pooled by virtue of the rates seen in Study 1100.1486 among treatment-naïve subjects. There were marginally greater rates of rash, headache, nausea and vomiting reported for NVP IR treatment groups (these rates driven again by Study 1100.1486) and a slightly greater frequency of diarrhea and fatigue in the NVP XR treatment groups (as driven by Study 1100.1526). In general, however, the two treatments are comparable with respect to AE rates and no new AEs emerged as significant (Table 24).

**Table 24: Adverse Events Occurring in ≥ 5% Subjects, Pooled Data (Study 1100.1486 and 1100.1526)**

Adverse event	Number of subjects (%)		
	NVP IR 200mg BID (N=654)	NVP XR 400mg QD (N=800)	Total (N=1454)
Nasopharyngitis	97 (15)	117 (15)	214 (15)
Diarrhea	67 (10)	88 (11)	155 (11)
Upper respiratory tract infection	56 (9)	68 (9)	124 (9)
Rash	50 (8)	55 (7)	105 (7)
Headache	62 (9)	52 (7)	114 (8)
Bronchitis	40 (6)	49 (6)	89 (6)
Fatigue	28 (4)	39 (5)	67 (5)
Nausea	51 (8)	38 (5)	89 (6)
Back pain	29 (4)	37 (5)	66 (5)
Cough	38 (6)	34 (4)	72 (5)
Hypertension	30 (5)	32 (4)	62 (4)
Vomiting	31 (5)	26 (3)	57 (4)

Source: AE dataset 1100.148 + 1100.1526

## 7.4.2 Laboratory Findings

### Study 1100.1486

The median change from baseline to last value on treatment for laboratory evaluations of interest (hematology, liver enzymes, chemistries, lipids) was comparable between the 2 treatment groups (data not shown). Most changes were generally small. There was no median change from baseline in creatinine for either group. (CD4 cell count changes are addressed in the efficacy portion of this review.)

With respect to DAIDS graded laboratory abnormalities (Table 25), most of these events were Grade 2 (moderate) and the rates of events were comparable between the two treatment groups. Grade ≥ 2 elevations of ALT and AST enzymes were reported in 90 (9%) subjects (IR 49 [10%]), XR 41 [8%]). Grade 4 AST or ALT abnormalities tended to occur with slightly greater frequency in the NVP IR group. In the initial weeks of therapy, there was a lower probability of Grade 3 or 4 ALT or AST elevations occurring in the NVP XR group than in the NVP IR group.

**Table 25: Laboratory Abnormalities ≥ Grade 2 that Represent Worsening from Baseline (Study 1100.1486)**

Laboratory test	DAIDS Toxicity Grade	Limit	Number of subjects (%)		
			NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Neutrophils	2	1,500-1,999/mm <sup>3</sup>	35 (7)	23 (5)	58 (6)
	3	1,000-1,499/mm <sup>3</sup>	12 (2)	7 (1)	19 (2)
	4	< 1,000/mm <sup>3</sup>	3 (1)	3 (1)	6 (1)
Platelets	2	50,000-99,999/mm <sup>3</sup>	7 (1)	8 (2)	15 (1)
	3	25,000-49,999/mm <sup>3</sup>	1 (<1)	0	1 (<1)
	4	< 25,000/mm <sup>3</sup>	0	0	0
ALT (U/L)	2	2.6-5.0 x ULN	52 (10)	46 (9)	98 (10)
	3	5.1-10.0 x ULN	17 (3)	15 (3)	32 (3)
	4	> 10.0 x ULN	17 (3)	11 (2)	28 (3)
AST (U/L)	2	2.6-5.0 x ULN	43 (9)	31 (6)	72 (7)
	3	5.1-10.0 x ULN	11 (2)	13 (3)	24 (2)
	4	> 10.0 x ULN	10 (2)	7 (1)	17 (2)
Bilirubin, total (mg/dL)	2	1.6-2.5 x ULN	7 (1)	4 (1)	11 (1)
	3	2.6-5.0 x ULN	4 (1)	4 (1)	8 (1)
	4	> 5.0 x ULN	1 (<1)	5 (1)	7 (1)
Alkaline Phosphatase (U/L)	2	2.6-5.0 x ULN	19 (4)	11 (2)	30 (3)
	3	5.1-10.0 x ULN	1 (<1)	4 (1)	5 (<1)
	4	> 10.0 x ULN	0	0	0
Amylase (U/L)	2	1.6-2.0 x ULN	24 (5)	19 (4)	43 (4)
	3	2.1-5.0 x ULN	20 (4)	13 (3)	33 (3)
	4	> 5.0 x ULN	0	1 (<1)	1 (<1)
Lipase (U/L)	2	1.6-3.0 x ULN	9 (2)	19 (4)	28 (3)
	3	3.1-5.0 x ULN	5 (1)	1 (<1)	6 (1)
	4	> 5.0 x ULN	1 (<1)	1 (<1)	2 (<1)
LDL (mg/dL)	2	160-190 mg/dL	74 (15)	65 (13)	139 (14)
	3	> 190 mg/dL	19 (4)	21 (4)	40 (4)
	4	N/A			
Cholesterol (mg/dL)	2	240-300 mg/dL	86 (17)	91 (18)	177 (18)
	3	> 300 mg/dL	15 (3)	10 (2)	25 (2)
	4	N/A			
Triglycerides (mg/dL)	2	500-750 mg/dL	10 (2)	17 (3)	27 (3)
	3	751-1,200 mg/dL	9 (2)	4 (1)	13 (1)
	4	> 1,200 mg/dL	1 (<1)	2 (<1)	3 (<1)
Creatinine Kinase	2	6.0-9.9 x ULN	16 (3)	19 (4)	35 (4)

	3	10.0-19.9 x ULN	12 (2)	16 (3)	28 (3)
	4	≥ 20.0 x ULN	13 (3)	14 (3)	27 (3)

Source: LB dataset

Gamma glutamyltransferase (GGT) enzymes are not part of in the DAIDS toxicity grading table. Furthermore, asymptomatic elevations in GGT levels are not a contraindication to continuing nevirapine therapy in the absence of elevations in other liver enzyme tests. In Study 1100.1146, GGT elevations above the upper limit of normal (ULN) occurred frequently (89%) and most of these were 1-2 x ULN or 2-5 x ULN. The rates of GGT elevations across all categories were slightly higher in the NVP IR group. Only 14% of subjects with GGT elevations had concomitant Grade ≥ 2 AST/ALT elevations, suggesting that most GGT elevations occurred in isolation.

Following a report from the FDA's Division of Scientific Investigations (DSI) regarding discrepancies between the reporting of elevated creatinine phosphokinase (CPK) levels as laboratory abnormalities and the reporting of such events as AEs, an analysis of the laboratory and AE data was carried out regarding elevated CPK reporting and the incidence of rhabdomyolysis. Elevations in CPK greater than ULN occurred in 63% of subjects, with equal distribution between the two treatment groups. DAIDS Grade 2-4 CPK elevations were also evenly balanced between both treatment arms. There were 27 subjects with DAIDS Grade 4 CPK elevations (IR 13 [3%], XR 14 [3%]); however, there were only 2 cases of rhabdomyolysis reported, one in each treatment arm (Subjects 12729 and 14718). Neither event of rhabdomyolysis was serious, but both were considered Grade 4 and were accompanied by Grade 4 CPK elevations. Both events occurred early in treatment. One case was not considered drug-related and treatment continued, whereas the other case was considered drug-related and treatment was interrupted. Both events resolved without sequelae. In sum, although elevated CPK levels up to Grade 4 were observed in about 3% of subjects, these laboratory abnormalities were evenly balanced between both treatment arms and were not generally associated with clinical adverse events.

There was a small median increase in cholesterol, LDL, and HDL levels from baseline to Week 48, whereas triglycerides levels decreased. Changes in lipid parameters from baseline, however, were similar between the two treatment groups. Use of lipid-lowering agents was comparable between the two groups (IR 4%, XR 3%).

#### Study 1100.1526

In Study 1526, Grade 2-4 laboratory abnormalities were rare, and those that were reported were balanced between the two treatment groups. Elevated transaminases or liver function tests (e.g. bilirubin, alkaline phosphatase) were not prominent findings. Lipid parameters, such as LDL or total cholesterol, were not reported in this trial, but triglycerides were, including four (1%) subjects with DAIDS Grade 4 triglyceride

elevations (IR 2, XR 2). There were a few reports of Grade 3/4 pancreatic enzyme elevations, more in NVP IR than the NVP XR group, but no cases of clinical pancreatitis were identified. Table 26 lists DAIDS Grade  $\geq 2$  laboratory abnormalities that were worse from baseline.

**Table 26: Laboratory Abnormalities  $\geq$  Grade 2 that Represent Worsening from Baseline (Study 1100.1526)**

Laboratory test	DAIDS toxicity grade	Limit	Number of subjects (%)		
			NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Neutrophils	2	1,500-1,999/mm <sup>3</sup>	4 (3)	8 (3)	12 (3)
	3	1,000-1,499/mm <sup>3</sup>	1 (1)	1 (<1)	2 (<1)
	4	< 1,000/mm <sup>3</sup>	0	0	0
Platelets	2	50,000-99,999/mm <sup>3</sup>	0	3 (1)	3 (1)
	3	25,000-49,999/mm <sup>3</sup>	0	0	0
	4	< 25,000/mm <sup>3</sup>	0	0	0
ALT (U/L)	2	2.6-5.0 x ULN	3 (2)	9 (3)	12 (3)
	3	5.1-10.0 x ULN	4 (3)	2 (1)	6 (1)
	4	> 10.0 x ULN	0	1 (<1)	1 (<1)
AST (U/L)	2	2.6-5.0 x ULN	6 (4)	6 (2)	12 (3)
	3	5.1-10.0 x ULN	1 (1)	2 (1)	3 (1)
	4	> 10.0 x ULN	0	0	0
Amylase (U/L)	2	1.6-2.0 x ULN	6 (4)	5 (2)	11 (3)
	3	2.1-5.0 x ULN	5 (3)	5 (2)	10 (2)
	4	> 5.0 x ULN	0	0	0
Lipase (U/L)	2	1.6-3.0 x ULN	4 (3)	9 (3)	13 (3)
	3	3.1-5.0 x ULN	3 (2)	1 (<1)	4 (1)
	4	> 5.0 x ULN	1 (1)	0	1 (<1)
Triglycerides (mg/dL)	2	500-750 mg/dL	8 (5)	11 (4)	19 (4)
	3	751-1,200 mg/dL	2 (1)	4 (1)	6 (1)
	4	> 1,200 mg/dL	2 (1)	2 (1)	4 (1)

Source: LB dataset

### 7.4.3 Vital Signs

Vital signs were obtained as part of the routine physical examination at study visits. Vital signs considered clinically important were reported as AEs and discussed as such in the appropriate sections of this review. In general, there were no clinically relevant

trends observed over time or between treatment groups for systolic or diastolic blood pressure or pulse rate.

#### 7.4.4 Electrocardiograms (ECGs)

No routine ECG monitoring was performed during the Phase 3 trials.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

As only one dose of nevirapine XR formulation was evaluated in the Phase 3 trials, analysis of dose dependency for AEs is not possible. However, no correlation was observed between trough levels and the incidence of adverse events.

#### 7.5.2 Time Dependency for Adverse Events

The significant AEs associated with nevirapine therapy are rash and hepatotoxicity. As noted in Section 7.3.4 (Significant Adverse Events) most rash events in Study 1100.1486 occurred either during the lead-in phase or shortly after randomization. Similarly, hepatic events occurred within the first 2 months of initiating therapy. The current USPI label for nevirapine already notes that the period of greatest risk for these events is in the first 18 weeks of treatment.

Study 1100.1521 is not suitable for a time dependency evaluation as all subjects were already on nevirapine therapy for at least 18 weeks prior to study entry.

#### 7.5.3 Drug-Demographic Interactions

Overall, AEs were reported with equal frequency among men and women in Study 1100.1486, both in the trial as a whole and during the randomization phase. In the randomized phase (n=1011), however, a larger proportion of women compared to men reported AEs within the NVP IR group (women 71/75 [95%] vs. men 381/431[88%]). In the NVP XR group, on the other hand, a smaller proportion of women than men reported AEs (60/74 [81%] vs. 383/431 [89%], respectively).

Looking at women only, there was a 14% greater proportion of AEs reported in the NVP IR group than in the NVP XR group. There was no such treatment difference observed among men. This trend of more women reporting AEs with NVP IR than NVP XR treatment was also seen with drug-related AEs, AEs leading to drug discontinuation, DAIDS 3 or 4 AEs and drug-related DAIDS 3 or 4 AEs. This treatment effect, however, was not seen with SAEs among women.

The USPI label for nevirapine indicates that women are at greater risk than men for rash and hepatic events and patients with higher baseline CD4 cell counts (> 400 cells/mm<sup>3</sup> for men and > 250 cells/mm<sup>3</sup> for women) are at greater risk than those with lower counts. Consistent with this, rash and hepatic events tended to occur more frequently in women than men. Moreover, the rates for these events were higher among women in the NVP IR group than in the NVP XR group.

In Study 1100.1486, there was a higher frequency of rash reported in women compared to men during the randomized phase (odds ratio [OR] = 1.38). The association between female gender and rash was more notable in the NVP IR group (OR=1.75). This association, however, was not seen in the lead-in phase (Table 27).

**Table 27: Drug-related Rash Events by Gender (Study 1100.1486)**

Phase	Treatment	Female (n/N [%])	Male (n/N [%])	Total
Randomized	NVP IR 200 mg BID	7/75 (9)	23/431(5)	30/506 (6)
	NVP XR 400 mg QD	5/74 (7)	27/431(6)	32/505 (6)
Total Randomized		12/149 (8)	50/862 (6)	62/1011 (6)
Lead-in		12/162 (7)	62/906 (7)	74/1068 (7)
Not randomized		7/13 (54)	27/42 (64)	34/55 (62)

Source: AE dataset

With respect to hepatotoxicity, women in Study 1100.1486 were twice as likely as men to have any of the following: any hepatic events, symptomatic hepatic events, and Grade 3/4 transaminase elevations (ORs = 2.19, 2.27, and 2.03, respectively). These results were based on logistic regression analysis conducted by the applicant on the adjudicated hepatic events dataset. The gender effect was only seen in the NVP IR group, however. None of the 74 women in the NVP XR group had a symptomatic event, whereas 5% (4/75) of women in the NVP IR group had a symptomatic event (compared to 2% of men in the NVP IR group). It is worth noting, however, that the overall number of symptomatic hepatic events in this trial was small (22 total: 4/149 (3%) in women, 18/862 [2%] in men); therefore, the significance of these findings is not clear. Nonetheless, a similar gender effect was seen in the NVP IR group for subjects with any

hepatic event and subjects with Grade 3/4 transaminase elevations, but no such effect was seen in the NVP XR group. In sum, data from Study 1100.1486 suggest a higher risk of hepatic events among women receiving NVP IR compared to men, but no such increased risk for women receiving NVP XR.

In Study 1100.1526, by contrast, there were only 3 rash events reported and all 3 occurred in men. Hepatic events were rare in this trial and none were deemed related to nevirapine therapy.

AE rates observed in subgroups defined by race or region were generally consistent with those observed for the overall study population in both Studies 1100.1486 and 1100.1526, suggesting no interaction between race/ethnicity and treatment.

#### 7.5.4 Drug-Disease Interactions

As noted above, women are at an increased risk for rash and hepatic events with initiation of nevirapine therapy compared to men. In a retrospective review, women with CD4 cell counts  $> 250$  cells/mm<sup>3</sup> had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4 cell counts  $< 250$  cells/mm<sup>3</sup> (11% versus 0.9%). An increased risk was observed in men with CD4 cell counts  $> 400$  cells/mm<sup>3</sup>, but the magnitude of the increased risk was not as great as in women

Although the protocol criteria for Study 1100.1486 excluded participants with CD4 cell counts above these thresholds, there were 6 women with CD4 cell count  $> 250$  cells/mm<sup>3</sup> and 21 men with CD4 cell count  $> 400$  cells/mm<sup>3</sup> treated in the trial. Given the small number of subjects with baseline CD4 cell counts above the prescribed limit, only a limited analysis of the interaction between baseline CD4 count and the incidence of rash or hepatic events can be carried out for Study 1100.1486.

Of the 24 women who had a rash event in Study 1100.1481, only 1 (4%) had a baseline CD4 cell count  $> 250$  cells/mm<sup>3</sup>. This subject (No. 10938) was randomized to the NVP IR arm, had a baseline CD4 cell count of 251 cells/mm<sup>3</sup>, and developed a Grade 3 maculo-papular rash on Day 9; she discontinued study drug as a result. Of the 112 men who developed rash, 1 (1%) subject in the lead-in phase and 3 (3%) in the randomized phase (IR 2, XR 1) had baseline CD4 cell counts  $> 400$  cells/mm<sup>3</sup>; one of these developed Grade 3 SJS requiring hospitalization in the randomization phase (Subject 17677 in the NVP IR group).

The incidence of hepatic events In Study 1100.1486 also correlated to baseline CD4 cell counts. In general, subjects with higher baseline CD4 cells counts were more likely to have a hepatic event, although the total number of symptomatic hepatic events was small (n=22). The association between hepatic events and CD4 cell count in this trial was not as strong as the observed gender effect.

In sum, although there are signs of increased risk for rash and hepatic events in subjects with CD4 cell counts above the cut-off, given the small number of cases, the clinical significance if these findings is not clear and comparison between treatment groups is difficult.

In Study 1100.1526, where 76% of subjects had CD4 counts > 400 cells/mm<sup>3</sup> and subjects had been on nevirapine therapy for at least 18 weeks prior to entry, rash or hepatic events were rare. These findings suggest no correlation between CD4 count at the time of switch and risk of developing major events in stable subjects switching from NVP IR to NVP XR.

#### 7.5.5 Drug-Drug Interactions

There were no new drug interaction studies conducted with nevirapine XR.

Background antiretroviral therapy in Study 1100.1526 did not appear to have a significant impact on AE rates or types of AEs.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

Long-term carcinogenicity studies for 2 years in animals have identified an increase in hepatocellular adenomas and carcinomas with nevirapine exposures lower than that seen in humans at the 200 mg BID dose. In the absence of genotoxic activity of nevirapine, the relevance of these findings to humans is not known. Post-marketing surveillance of nevirapine has not identified an association with carcinogenicity in humans.

In the Phase 3 trials for NVP XR, excluding benign skin neoplasms, there were 10 malignancies reported among 18 subjects: Kaposi's sarcoma (9), B-cell lymphoma (1), recurrent bladder cancer (2), breast neoplasm (1), malignant melanoma (1), Non-Hodgkin's lymphoma (1), uterine cancer (1), thyroid neoplasm (1), and prostate cancer (1). Fourteen of these cases occurred in Study 1100.1486 and four in Study 1100.1526. None of these cases were considered drug-related, except for the thyroid neoplasm (nodular) which occurred on Day 276 of NVP IR therapy in Study 1486 in a 38-year-old African subject (Subject 16568). The majority of these cases occurred within 6 months

of start of trial, with the exception of the melanoma, breast cancer, thyroid neoplasm, and Non-Hodgkin's lymphoma cases.

### 7.6.2 Human Reproduction and Pregnancy Data

A total of 10 pregnancies occurred in the course of the two Phase 3 trials: 9 in Study 1100.1486 and 1 in Study 1100.1526.

In Study 1486, one subject became pregnant and discontinued treatment during the lead-in period; the other 8 pregnancies occurred after randomization (IR 1, XR 7). All pregnant subjects except 3 discontinued from Study 1100.1486. Two subjects continued, but one had an elective abortion (NVP IR) and another had a spontaneous abortion (NVP XR). A third subject remains on study drug (NVP XR) and was still pregnant at the time of database lock.

Of the 6 pregnant women who discontinued from Study 1100.1486, follow-up information is available for 4 subjects; the other 2 were lost to follow-up. Among these 4 women, 3 had normal full term pregnancies and 1 had premature rupture of membranes at 26 weeks gestation.

In Study 1100.1526, there was 1 pregnancy in the NVP XR group. This subject discontinued from study and then experienced a spontaneous abortion after 4 weeks of carriage.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric trials are deferred and will be submitted following approval of the adult product. No assessment of effects on growth was conducted in the adult population.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Three subjects in Study 1100.1526 experienced overdose with NVP XR when double the dose was given in error. These cases were asymptomatic and were not accompanied by elevations in liver enzymes.

Cases of nevirapine overdose have previously been reported with doses ranging from 800 to 1600 mg per day for up to 15 days. Patients have experienced edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increased transaminases, and weight loss. All symptoms subsided following discontinuation of nevirapine.

Nevirapine has not been observed to have the potential for abuse. No new information relating to the drug abuse potential of NVP XR was observed in the clinical development program for NVP XR. No data relating to withdrawal and rebound from NVP XR are currently available.

## **7.7 Additional Submissions / Safety Issues**

In the Phase 3 trials for NVP XR, a total of 15 (2%) subjects from across both trials (n=800) reported the appearance of residual remnants of drug product in their stools. These cases were reported from different investigator sites around the globe. The drug remnants were reportedly soft and hydrated. Viral load and CD4 cell counts for subjects in these cases remained stable and acceptable plasma PK levels were maintained throughout. All subjects met the primary endpoint of their respective trials. A letter describing these observations was sent to all investigators in the NVP XR trials in July 2009.

## **8 Postmarket Experience**

The immediate-release formulation of nevirapine (Viramune®) was first approved in the U.S. in 1996 for the treatment of HIV-1 infection. NVP IR 200 mg tablets are currently widely available. The USPI for Viramune contains the postmarketing experience with the immediate-release formulations of nevirapine since approval. NVP XR is not yet marketed and no additional review of postmarketing events was performed.

## 9 Appendices

### 9.1 Literature Review/References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011.
2. Poveda E, Garrido C, de Mendoza C, et al. Prevalence of etravirine (TMC125) resistance mutations in HIV-infected patients with prior experience of non-nucleoside reverse transcriptase inhibitors. *J Antimicrob Chemother* 2007; 60:1409-10.

### 9.2 Labeling Recommendations

The proposed USPI label for VIRAMUNE XR tablets used labeling for VIRAMUNE® tablets and oral suspension approved June 2010 as a template. Changes were made to Section 2.1 (*Dosage and Administration*), Section 3 (*Dosage Forms and Strength*) and Section 17.2 (*Patient Counseling Information - Administration*) to provide dosing instructions specific to the XR formulation. Likewise, changes were made to Section 6.1 (*Clinical Trials Experience*), Section 12.4 (*Microbiology*), and Section 14 (*Clinical Studies*) to present the clinical trial findings from the nevirapine XR program (Studies 1100.1486 and 1100.1526). The SNAPSHOT method (see Table 9 of this review) was used to display the Week 48 outcomes for the pivotal trial, Study 1100.1486, in Section 14. Corresponding changes were made to the Highlights Sections.

Discussion between FDA and the applicant resulted in the removal of [REDACTED] (b) (4)

[REDACTED] In addition, the *Warnings and Precautions* section of the Highlights was modified to concentrate the key safety information into 3 bullet items: rash, hepatotoxicity and ARV class effects. The review team made other minor edits throughout the document to make the material easier to read and comprehend.

Aside from the changes described above, the rest of the approved VIRAMUNE® label, including the black box warning, was not significantly altered in the process of creating the new VIRAMUNE XR label, as there was no new information to report or the information found in those sections was related to the nevirapine active ingredient.

Clinical Review  
Peter S. Miele, M.D.  
NDA 201152  
VIRAMUNE XR (nevirapine extended-release)

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### **9.3 Advisory Committee Meeting**

Review and approval of this application did not warrant convening an Advisory Committee Meeting.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PETER S MIELE  
02/27/2011

LINDA L LEWIS  
02/27/2011

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 201152**

**Applicant: Boehringer  
Ingelheim**

**Stamp Date: June 3, 2010**

**Drug Name: VIRAMUNE XR  
(nevirapine extended-release  
tablets)**

**NDA/BLA Type: Standard  
Review**

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	<input checked="" type="checkbox"/>			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	<input checked="" type="checkbox"/>			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	<input checked="" type="checkbox"/>			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	<input checked="" type="checkbox"/>			
5.	Are all documents submitted in English or are English translations provided when necessary?	<input checked="" type="checkbox"/>			
6.	Is the clinical section legible so that substantive review can begin?	<input checked="" type="checkbox"/>			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	<input checked="" type="checkbox"/>			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	<input checked="" type="checkbox"/>			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	<input checked="" type="checkbox"/>			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	<input checked="" type="checkbox"/>			
11.	Has the applicant submitted a benefit-risk analysis for the product?	<input checked="" type="checkbox"/>			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?  <u>Study Number:</u> 1100.1489  <u>Study Title:</u> Steady state bioavailability of 2 different nevirapine extended release formulations compared to steady state 400 mg of Viramune® (200 mg BID), in HIV-1 infected subjects, an open label, non randomized, multidose and multistage parallel group study (ERVIR)	<input checked="" type="checkbox"/>			

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Sample Size: 92</p> <p>Study design: Open-label, multi-stage, four parallel group design</p> <p>Arms:                      NVP XR 300 mg KCR 20% (n=23)                      NVP XR 300 mg KCR 25% (n=21)                      NVP XR 400 mg KCR 20% (n=24)                      NVP XR 400 mg KCR 25% (n=24)</p> <p>Location in submission: Module 5.3.3.2</p>				
<b>EFFICACY</b>					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p><u>Pivotal Study #1 1100.1486</u></p> <p>“A randomized, double blind, double dummy, parallel group, active controlled trial to evaluate the antiviral efficacy of 400 mg QD nevirapine Extended Release formulation in comparison to 200 mg BID nevirapine immediate release in combination with Truvada® in antiretroviral therapy naïve HIV-1 infected patients (VERxVE)”</p> <p>Indication: treatment of HIV-1 infection</p> <p><u>Supportive Study #2 1100.1526</u></p> <p>“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 (TRANxITION)”</p> <p>Indication: treatment of HIV-1 infection</p>	<input checked="" type="checkbox"/>			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	<input checked="" type="checkbox"/>			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	<input checked="" type="checkbox"/>			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		<input checked="" type="checkbox"/>		The applicant will be asked to submit a rationale.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner	<input checked="" type="checkbox"/>			

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			<input checked="" type="checkbox"/>	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	<input checked="" type="checkbox"/>			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?		<input checked="" type="checkbox"/>		The overall extent of exposure for nevirapine XR was 1134 subjects. In Phase III studies, 800 patients received the final 400 mg nevirapine XR formulation proposed for registration (which is below the ICH recommended 1500), 736 patients for at least 24 weeks, 423 for at least 48 weeks, and 165 for at least 72 weeks. However, there is sufficient accumulated data regarding nevirapine exposure from use of the IR formulation that the submitted safety database is considered adequate.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			<input checked="" type="checkbox"/>	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?				MedDRA (Version 12.1)
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	<input checked="" type="checkbox"/>			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	<input checked="" type="checkbox"/>			
<b>OTHER STUDIES</b>					

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	<input checked="" type="checkbox"/>			<ul style="list-style-type: none"> <li>• comparison of viral load assays (Roche Cobas TaqMan assay and Amplicor)</li> <li>• evaluation the phenotypic and genotypic resistance to nevirapine</li> </ul>
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			<input checked="" type="checkbox"/>	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	<input checked="" type="checkbox"/>			Deferral and partial waiver for pediatric studies in children less than 3 years of age
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	<input checked="" type="checkbox"/>			
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		<input checked="" type="checkbox"/>		The applicant will be asked to submit a rationale.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	<input checked="" type="checkbox"/>			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	<input checked="" type="checkbox"/>			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	<input checked="" type="checkbox"/>			
34.	Are all datasets to support the critical safety analyses available and complete?	<input checked="" type="checkbox"/>			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	<input checked="" type="checkbox"/>			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	<input checked="" type="checkbox"/>			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			<input checked="" type="checkbox"/>	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	<input checked="" type="checkbox"/>			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input checked="" type="checkbox"/>			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES**

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

1. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

Peter S. Miele, M.D.	July 8, 2010
Reviewing Medical Officer	Date
Linda L. Lewis, M.D.	July 21, 2010
Clinical 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

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

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/s/

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PETER S MIELE  
07/21/2010

LINDA L LEWIS  
07/23/2010