21 July 2011
EMA/538380/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Viramune

(nevirapine)

Procedure No.: EMEA/H/C/000183/X/95

Note

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

ABC	Abacavir
AE	Adverse event
AIDS	Aquired Immune Deficiency Syndrome
ALT	Alanine-aminotransferase
Amplicor	Cobas Amplicor HIV-1 Monitor Version 1.5 Ultrasensitive assay
ARV	Antiretroviral
AST	Aspartate-aminotransferase
AUC	Area under the plasma concentration curve
AUC0-∞	Area under the plasma concentration curve from time zero to infinity
AZT	Azidothymidine (also called zidovudine or ZDV)
BI	Boehringer-Ingelheim
BID	Bis in die (twice daily)
BMI	Body Mass Index
CD4+	Cluster designation 4 positive (antigen marker on T-cells)
CI	Confidence interval
C_{min}	Concentration at minimum (or trough) level
$C_{min,ss}$	Concentration at minimum (or trough) level at steady state
C_{max}	Concentration at maximum (or peak) level
CTR	Clinical Trial Report
DAIDS	Division of AIDS, National Institutes of Health
DAVP	Division of Antiviral Products
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ESRD	End Stage Renal Disease
EU	European Union
FAS	Full analysis set
FTC	Emtricitabine
HAART	Highly active anti-retroviral therapy
HDL	High Density Lipoprotein

HIV-1	Human Immunodeficiency Virus, Type 1
HPMC	Hypromellose or hydroxypropylmethyl cellulose polymer
IR	Immediate release
Kg	Kilogram
LFT	Liver function test
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
n	Number
NDA	New drug application
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitors
NVP	Nevirapine
OR	Odds Ratio
PK	Pharmacokinetics
PPS	Per Protocol Set
pVL	Plasma Viral Load
RT	Reverse Transcriptase
QD	Quaque die (once daily)
SAE	Serious Adverse Event
SOC	System Organ Class
TaqMan	Roche Cobas TaqMan assay
TDF	Tenofovir
TLOVR	Time to Loss of Virologic Response
T_{max}	Time Corresponding to C_{max}
ULN	Upper Limit of Normal
XR	Extended Release
3TC	Lamivudine

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH. submitted on 18 August 2010 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Viramune 50 mg, 100 mg and 400 mg prolonged-release tablets, through the centralised procedure pursuant to article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2. (c) addition of a new strength and 2. (d) addition of a new pharmaceutical form).

The applicant applied for the following indication:

"Viramune is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age (see section 4.4.).

Most of the experience with Viramune is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Viramune should be based on clinical experience and resistance testing (see section 5.1)."

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/26/2010 for the following condition(s): Human immunodeficiency virus (HIV-1) infection

The PIP is completed.

The PDCO issued an opinion on compliance (EMA-C-000391-PIP01-08-M01).

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 20 September 2007. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Viramune has been given a Marketing Authorisation in the European Union since 5 February 1998.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Beatriz Silva Lima Co-Rapporteur: Pieter Neels

- The application was received by the EMA on 18 August 2010.
- The procedure started on 22 September 2010.
- The Joint Rapporteur /Co-rapporteur initial Assessment Report was circulated to all CHMP members on 3 January 2011.
- During the meeting on 20 January 2011 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2011.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 07 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 May 2011.
- During the CHMP meeting on 16-19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 07 June 2011.
- During the meeting in July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Viramune 50 mg, 100 mg and 400 mg prolonged-release tablets on 21 July 2011.

2. Scientific discussion

2.1. Introduction

The current guidelines for antiretroviral (ARV) treatment of HIV infection recommend initial treatment with a combination of 3 drugs, 2 of which should be nucleoside / nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) and a third drug that may be a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor. Studies have demonstrated the therapeutic benefit of a NNRTI-combined regimen including nevirapine. In addition, several published studies revealed that the primary factor leading to long term treatment success was adherence to treatment along with the potency of the drug combination. In order to increase adherence, once a day treatment regimens are now favoured by both physicians and patients.

Nevirapine was developed as the first non-nucleoside reverse transcriptase inhibitor (NNRTI). 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. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ or δ) are not inhibited by nevirapine.

The efficacy of nevirapine was demonstrated in adequate and well controlled clinical studies to support approval for use in HIV infected patients at 200 mg BID in the US and in the European Union (EU). Since then, BI and external investigators have continued to study the safety and efficacy of nevirapine.

Nevirapine tablets (immediate release [IR]) received first marketing authorization in the USA in June 1996 (marketed as Viramune) and subsequently in the European Union in February 1998 through the centralised procedure. An oral suspension formulation was firstly approved in the US in September 1998 and in the European Union in June 1999. Subsequent approvals for the tablets and the oral suspension have been obtained in over 100 countries.

The nevirapine XR programme was developed to improve treatment convenience, and thus, potentially adherence, by providing once daily administration, while maintaining the efficacy provided by an adequate Cmin,ss as well as safety.

Based on the 2NN study efficacy and pharmacokinetic data, the Marketing Authorisation Holder for Viramune developed a strategy for development of a prolonged release formulation in adults and children, targeting a reduced nevirapine exposure with a lower nevirapine Cmax and AUC while maintaining adequate nevirapine Cmin levels. In adults, the target PK profile of the prolonged release formulation was a median Cmin,ss of 3 µg/ml +/- 0.5 (>15 fold higher than the IC95 for wild type-

virus [710nM]) with a Cmax/Cmin ratio <1.5. In the paediatric population, the applicant targeted comparable PK parameters. Based on these PK data, the nevirapine XR formulation was expected to produce at least comparable efficacy and safety to the marketed product as described previously (P06-05584).

Based on these hypotheses and objectives, the clinical programme was developed to examine different XR formulations, test and verify the pharmacokinetic characteristic of each of them and select the final formulation for confirmatory testing in an adequately powered placebo-controlled, randomised study in treatment-naïve HIV-1 infected adult patients, as well as in a comparative clinical study of adult patients switching over from nevirapine IR to Nevirapine XR. This programme includes the first major study of >1000 randomised patients that has applied the CD4+ thresholds prospectively.

Nevirapine XR tablet was investigated to support the same therapeutic indication as the nevirapine IR tablet.

2.2. Quality aspects

2.2.1. Introduction

By this extension procedure, a new pharmaceutical form – prolonged-release tablet – is introduced. Three strengths of the product, 50 mg, 100 mg and 400 mg, were developed. They are yellow, distinguished by shape and debossing: the 50 mg tablets are round, biconvex with "V5" on one side and "BI" on the other; the 100 mg strength is round, biconvex, debossed with "V01" on one side and BI tower logo on the other side and the 400 mg tablets are oval, biconvex, debossed with "V04" on one side and BI tower logo on the other side.

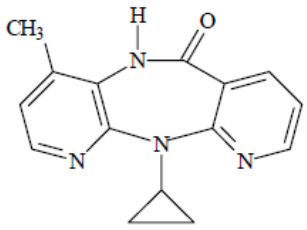
The prolonged-release tablets are composed of the active substance nevirapine (in anhydrous form) and excipients, defined in the SmPC Section 6.1.

The tablets are packaged in HDPE bottles and PVC/alu blisters (400 mg strength only).

2.2.2. Active Substance

The active substance, nevirapine, anhydrous is identical to the substance already authorised in Viramune immediate-release tablets 200 mg. The active substance's physicochemical properties, synthesis, controls, and stability are fully described in the approved marketing authorization application for the 200 mg tablets. Reference is therefore made to this approved information.

Figure 1:



The drug substance is classified as a Biopharmaceutics Classification System (BCS) Class II compound due to its low solubility and high intestinal permeability. Nevirapine is a weak base and solubility within the physiologic range is strongly pH dependent, with increased solubility at acidic pH.

Particle size is controlled in the drug substance specification.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Formulation development focused on the adult strength 400 mg prolonged-release tablets. All three strengths, 50 mg, 100 mg, and 400 mg, have identical relative proportion of excipients. Thus, the formulation studies, while performed for the 400 mg, also apply directly to the lower strength tablets, intended for paediatric use.

All excipients in the nevirapine prolonged-release tablets are of compendial quality and are commercially available. The excipients selected for the formulation are: lactose monohydrate as a soluble diluent; hypromellose; magnesium stearate (vegetable origin) as a lubricant; purified water as a granulating agent and iron oxide yellow (E172) as a colorant.

A hydrophilic matrix system tablet design was developed using hypromellose (HPMC) as the rate-controlling polymer. Hypromellose is a methyl- and hydroxypropyl- mixed ether of cellulose and is differentiated based on its substitution type, in a range of viscosities. During a series of formulation studies, several types of prototype tablets were designed.

Hypromellose is commonly used in modified release products. The polymer is uniformly incorporated throughout the tablet. Upon contact with water, the polymer hydrates on the outer tablet surface to form a gel layer. The rate controlling mechanism for drug release *in vivo* is tablet erosion.

Compatibility of nevirapine with hypromellose and the other formulation components lactose, magnesium stearate and yellow iron oxide was confirmed.

Adventitious agents

The only excipient of human or animal origin is lactose monohydrate. All appropriate information on TSE safety for this excipient was provided.

Manufacture of the product

The manufacturing process for nevirapine prolonged-release tablets is a conventional high shear wet granulation process, followed by fluid bed drying, milling, final blending, and compression into tablets using a rotary tablet press. In-process controls include loss on drying in granulate and weight, hardness, thickness and friability of final tablets. The description of the manufacturing process is now sufficient, after updates requested during the evaluation process.

The manufacturing process validation of Nevirapine prolonged-release tablets was performed with three successive full production scale batches of Nevirapine 50 mg and 100 mg prolonged-release tablets and six full production scale batches of Nevirapine 400 mg prolonged-release tablets.

Product specification

The specification for all strengths of the finished product includes standard testing parameters typical for this kind of dosage form. The finished product is tested for identification, description, assay, degradation products, uniformity of dosage units by mass variation and dissolution. The specification tests and limits are acceptable.

Impurities/degradation products have been evaluated and found to be acceptable from the safety perspective.

Analytical methods used for the finished product control were sufficiently described and appropriately validated.

Batch results confirm compliance with the proposed product specifications and show good manufacturing consistency.

The dissolution method used was discussed during the procedure. The applicant does not use sink conditions for the highest strength; in addition, phosphate buffer with pH of 6.8 was used as the medium instead of acidic conditions, with 2% of sodium dodecyl sulphate (SDS). A clarification was requested to justify these parameters.

Due to prolonged-release characteristics of the tablets, the predominant environment where the tablet would be absorbed is small intestine, thus justifying pH of the media to be 6.8. Dissolution in the acidic conditions at pH 1 (without SDS) was examined and found to be much slower than in the pH 6.8 and incomplete after 24 hours in contrast to the *in vivo* behaviour. No dose dumping is seen. The choice of pH 6.8 was therefore fully supported.

Biorelevance of the dissolution test was also studied. The release rate from 50 mg tablets is faster than from 100 mg and 400 mg prolonged-release tablet, depending on the tablet volume and surface area; this was proved *in vivo* by pharmacokinetic studies. The *in vitro* dissolution behaviour of the product was extensively tested, using different media volumes and SDS concentrations. SDS in the concentration of 2% adds discriminatory value to the dissolution method used and reflects release rate of the active substance in plasma. The sink conditions for the 400 mg tablets were not considered optimal by the applicant, as the applicant considered more important to have a biorelevant test closely simulating the environment in the gastrointestinal tract rather than artificially imposed sink conditions

The assessment of the applicant's responses confirmed that the dissolution method is correctly chosen on the basis of physiologic relevancy and correlation to *in vivo* pharmacokinetic results.

Stability of the product

The stability studies are carried out in accordance with the current ICH/CHMP guidelines. All tests were carried out by validated, stability indicating analytical methods. The parameters tested are description, assay, dissolution and degradation products. In addition, tablet hardness, loss on drying and microbial quality were monitored for purposes of product characterisation.

Prolonged-release tablets of all three strengths were placed on stability, three pilot batches (400 mg) or three full scale batches (50 mg and 100 mg) per strength.

Accelerated studies (40ºC/75% RH) have been completed for all monitored batches. At present 12-month long-term stability results (at 25ºC/60% RH) are available for 50 mg and 100 strengths in HDPE bottles and 6-month results are available for 400 mg strength in both HDPE bottles and PVC/alu blisters. No significant changes or trends were observed so far. All results comply with the shelf-life specifications.

Results from stress studies and photostability studies show that the product does not need any special storage conditions.

Based on in-use stability study, the product should be used by 2 months from the first opening of the bottle.

The results support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major objections related to quality were raised during the assessment of this extension application. All other concerns were satisfactorily addressed by the applicant. The quality of the product is considered satisfactory.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

No further non-clinical development was considered necessary.

All non-clinical data available to date for nevirapine do not change the positive benefit-risk ratio.

Ecotoxicity/environmental risk assessment

The market introduction of this new pharmaceutical form, Viramune prolonged-release tablets, developed to offer long-term treated HIV-1 patients a once-a-day formulation for their convenience, without a proposal for new indications and without a change in total daily dose, will not result in a significant increase of environmental exposure to the drug substance, nevirapine and thus an updated ERA is not necessary as part of the application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

The clinical development programme of nevirapine XR for the proposed indication included three Phase I studies (Studies 1100. 1484, 1100. 1485 and 1100.1489) and two Phase III studies (Study 1100. 1486, in treatment-naïve adults, and Study 1526, in adults switching from IR to XR).

The Phase I studies determined the intestinal absorption of nevirapine, the PK profile, and the optimal formulation.

Three additional Phase I studies were designed to support the use of nevirapine XR in children. Two of these were single-dose PK studies in adult healthy volunteers (Studies 1100. 1517 and 1100.1531) and evaluated the pharmacokinetics, extended release characteristics and bioavailability of the

paediatric formulation (50 and 100 mg tablets). This was followed by a steady state pharmacokinetic study in nevirapine IR treated HIV-1 infected children (Study 1100.1518).

The following tables summarize the most relevant clinical studies.

Table 1

Study ID	Number of Study Centers/ Locations	Study Start/ Enrollment Status / Total Enrollment	Design / Control Type	Study Objective	Study & Control Drugs Dose, Route & Regimen	No. of Patients, by Treatment Group, Randomized/ Completed Week 48	Duration	Gender M/F/ Median Age (Range)	Diagnosis/ Inclusion Criteria	Primary Endpoint
1100.1486 [U10-3212-01, Module 5.3.5.1]	175 centers in 20 countries: Australia Argentina Belgium Botswana Canada France Germany Italy Ireland Mexico Netherlands Portugal South Africa Spain Switzerland Poland Russia Romania UK US	Study initiated on 15-NOV-2007; a total of 1068 patients entered; last patient entered on 24-NOV-2008	Randomized, double-blind, double dummy, parallel-group, active-control study	To evaluate the efficacy of 400 mg QD nevirapine extended release (XR) formulation versus 200 mg BID nevirapine immediate release (IR) with background Truvada® in ARV therapy-naïve HIV-1 infected patients after 48 weeks of treatment.	Study drug: nevirapine XR 400 mg QD, Oral Control drug: nevirapine IR, 200 mg BID, Oral	508 nevirapine IR 200 mg BID, 505 nevirapine XR 400 mg QD/ 409 nevirapine IR 200 mg BID, 421 nevirapine XR 400 mg QD	48 weeks with an extension through 144 weeks	Nevirapine IR 200 mg BID: M433/F75, 37.0 y, 18 to 68 y; nevirapine XR 400 mg QD; M431/F74, 38.0 y, 19 to 71 y	HIV-1 infected, ARV treatment-naïve adult patients	Sustained virologic response at Week 48

Table 2

Study ID	Number of Study Centers / Locations	Study Start/ Enrollment Status / Total Enrollment	Design/ Control Type	Study Objective	Study & Control Drugs Dose, Route & Regimen	No. of Patients, by Treatment Group, Randomized/ Completed Week 24	Duration	Gender M/F/ Median Age (Range)[a]	Diagnosis/ Inclusion Criteria	Primary Endpoint
1100.1526 [U10-3028-01, Module 5.3.5.1]	39 centers in 4 countries: Germany France UK US	Study initiated on 06-JAN-2009; a total of 445 patients entered; the last patient entered on 20-FEB-2009	Open-label, randomized, parallel-group, active-control study	To demonstrate the efficacy of a nevirapine XR-based regimen for HIV-1 infected patients who received a nevirapine IR-based regimen for at least 18 prior weeks of therapy.	Study drug: nevirapine XR 400 mg QD, Oral Control drug: nevirapine IR, 200 mg BID, Oral	149 nevirapine IR 200 mg BID, 296 nevirapine XR 400 mg QD / 144 nevirapine IR 200 mg BID, 288 nevirapine XR 400 mg QD	48 weeks with an extension through 144 weeks	Nevirapine IR 200 mg BID: M128/F20, 46.0 y, 27 to 71 y; nevirapine XR 400 mg QD; M244/F51, 46.0 y, 22 to 78 y	HIV-1 infected subjects treated with a Viramune®-based regimen for at least 18 prior weeks of therapy	Sustained virologic response through Week 24

[a] For study 1100.1526, although 149 and 296 patients were randomized to the nevirapine IR and XR groups, respectively, demographic data were available for the 148 and 295 patients who received study treatment in the nevirapine IR and XR groups, respectively.

Table 3

Study ID	Number of Study Centers / Locations	Study Start/ Enrollment Status / Total Enrollment	Design/ Control Type	Study Objective	Study & Control Drugs Dose, Route & Regimen	No. of Patients, by Treatment Group, Randomized/ Completed Week 24	Duration	Gender M/F/ Median Age (Range)[a]	Diagnosis/ Inclusion Criteria	Primary Endpoint
1100.1518 [U10-3350-01, Module 5.3.3.2]	10 centers in 4 countries: Botswana Germany S Africa US	Study initiated on 19-MAY-2009; a total of 85 patients entered; the last patient entered on 18-DEC-2009	Open-label, cross-over study PK study stratified by paediatric age group with a 10-day run-in phase, a 10-day PK phase, and an optional extension treatment phase	To evaluate steady-state PK of nevirapine XR in HIV-1 infected paediatric patients who had received a nevirapine IR-based regimen for at least 18 prior weeks of therapy.	Study drug PK phase: nevirapine XR 100 or 400 mg tablets in doses of 200, 300, or 400 mg QD, Oral Control drug run-in phase: nevirapine IR, BID, Oral	PK study of 22 days: Total 85 entered (E), 80 completed (C) By age group: 3 to <6 years 26 E, 25 C; 6 to <12 years 26 E, 24 C: 12 to <18 years 33 E, 31 C	10 days nevirapine IR run-in; 10 days nevirapine XR for PK Optional extension phase available; one patient treated with nevirapine XR for 208 days	M38/F47: 26 patients 3 to <6 y: 26 patients 6 to <12 years; 33 patients 12 to <18 years	HIV-1 infected paediatric patients treated with a Viramune®-based regimen for at least 18 prior weeks of therapy	Trough concentration at steady state of nevirapine XR

2.4.2. Pharmacokinetics

Absorption

- Bioavailability

Trial 1100.1484:

A single dose, 2-part, open-label, randomised, pharmacoscintigraphic investigation into the absorption of nevirapine when released into different parts of the gastro-intestinal tract

Objective:

To determine the absorption of nevirapine from different regions of the gastro-intestinal tract

Method:

The study compared the bioavailability of nevirapine when delivered to the following regions of the gastrointestinal tract: ascending colon, descending colon, ileum and jejunum. A comparator arm was included, in which a solution was given orally. The test product, 50 mg of nevirapine (suspended in 1 ml of pH 2 0.1M phosphate buffer), was delivered to different regions of the gastrointestinal tract by EnterionTM capsule. Movement of the EnterionTM capsule through the gut was assessed by incorporating an 111In (1MBq) marker in the radioactive tracer port of the capsule; this marker remained in the device throughout gastrointestinal transit. In order to provide an outline of the anatomy of the gastrointestinal tract 30mL of water administered with the capsule contained 4 MBq of radiolabelled marker (99mTc-DTPA).The different treatments are:

Treatment A: 50 mg Nevirapine (suspended in 1mL of pH2, 0.1M phosphate buffer) administered orally in 100 mL water.

Treatment B: 50 mg Nevirapine (suspended in 1mL pH2, 0.1M phosphate buffer) administered to the ascending colon*, *via* Enterion™ capsule.

Treatment C: 50 mg Nevirapine (suspended in 1mL pH2, 0.1M phosphate buffer) administered to the jejunum, *via* Enterion™ capsule.

Treatment D: 50 mg Nevirapine (suspended in 1mL pH2, 0.1M phosphate buffer) administered to the ileum *via* Enterion™ capsule.

Treatment E: 50 mg Nevirapine (suspended in 1mL pH2, 0.1M phosphate buffer) administered to the descending colon#, *via* Enterion™ capsule.

* ascending colon defined as the absorptive section of the large bowel, i.e. caecum, ascending colon, hepatic flexure.
# descending colon defined as the storage region of the large bowel, i.e. splenic flexure, descending colon and sigmoid colon.

For quantitation of drug plasma concentrations, blood was collected at the following time points: pre-dose, 5, 15 and 30 minutes and 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours post-dose/activation.

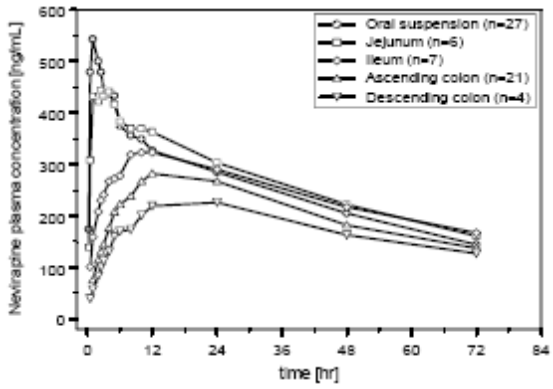
Results:

The mean gastric emptying time of capsules ranged from 0.88-3.35 h. The small intestinal and colon transit time ranged from 4.08-7.76 h and 17.6-21.2 h, respectively, and capsule recovery time ranged from 27.6-34.4 h. The relative bioavailability ratio of nevirapine in the jejunum was 1.06 (90% CI 1.00-1.12) compared to suspension dosing. In ileum, ascending, and descending colon, bioavailability decreased to 0.89 (0.80-0.99), 0.82 (0.71-0.95), and 0.58 (0.22-1.53), respectively. The absorption rate decreased (see Figure and table below) by about 10-fold from jejunum (3.83 h-1) to descending colon (0.338 h-1) and tmax increased from 2.42 h (jejunum) to 16.3 h (descending colon).

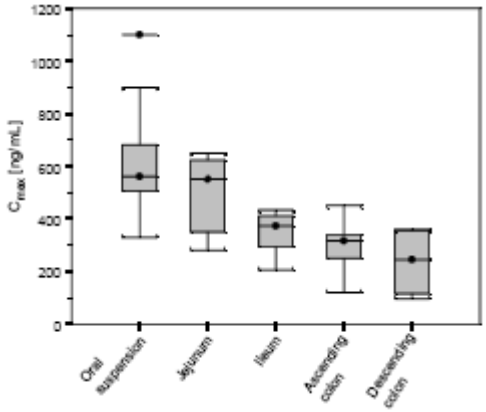
Problems occurred for capsule activations at the different locations. This resulted in a number of protocol deviations as well as an exposure to drug during treatment periods smaller or larger than initially planned.

It is clearly stated in the report that this study was a qualitative study to investigate the regional absorption of nevirapine. The results of the study indicate that nevirapine is absorbed from all sites in the gastrointestinal tract that were studied, i.e. jejunum, ileum, ascending colon and descending colon (see table below). Relative bioavailability decreased in the order oral administration of a suspension by mouth>administration in the jejunum> administration in the ileum>administration in the ascending colon>administration in the descending colon. The rate of nevirapine absorption decreases from the jejunum to the descending colon.

Figure 2:



Mean nevirapine plasma concentration-time profiles after administration of 50 mg nevirapine orally as suspension or via remotely-controlled capsules in ileum, jejunum, ascending colon, or descending colon



Comparison of Cmax of nevirapine after administration of 50 mg nevirapine by oral (n = 27), jejunum (n = 6), ileum (n = 7), ascending colon (n = 21), and descending colon (n = 4) routes

Table 4: Geometric mean ratios (point estimates) and 90% CI for nevirapine pharmacokinetics parameters after single administration of 50 mg nevirapine.

Parameter	N	Test	Reference	Adjusted gMean Ratio (Test/Reference)	Two sided 90 % Confidence Interval	
					Lower limit	Upper limit
C_{max} [ng/mL]	21	Oral	Ascending colon	0.45	0.39	0.51
	6	Oral	Jejunum	0.74	0.59	0.941
	7	Oral	Ileum	0.55	0.45	0.67
	4	Oral	Descending colon	0.29	0.12	0.66
$AUC_{0\text{-inf}}$ [ng·h/mL]	21	Oral	Ascending colon	0.82	0.711	0.945
	6	Oral	Jejunum	1.055	0.997	1.118
	7	Oral	Ileum	0.888	0.799	0.986
	4	Oral	Descending colon	0.583	0.221	1.534

Source data: Table 15.5.3: 2

Conclusion:

This study confirms that nevirapine was absorbed throughout the intestinal tract. Absorption of 82% was observed from the ascending colon, and these results seem to support the development of a prolonged release formulation of nevirapine.

Trial 1100.1485:

Relative bioavailability of different nevirapine prolonged release formulations compared to 200 mg of nevirapine oral tablet following oral administration in healthy male volunteers; an open-label, not randomized, parallel group study.

Objective:

To determine the relative bioavailability of different oral nevirapine extended release (XR) formulations compared to nevirapine immediate release (IR) tablet as well as to establish a level A in vitro/in vivo correlation (study u07-3362)

Method:

The pharmacokinetics of extended release formulations were assessed in a parallel group study with 17 healthy volunteers per dose group and compared with corresponding in vitro dissolution data obtained using a USP apparatus Type 1. In vitro samples were analyzed using HPLC with UV detection and in vivo samples were analyzed using a HPLC MS/ MS assay; the IVIVC analyses comparing the two results were performed using WinNonlin v5.2. The primary pharmacokinetic endpoints were AUC0-∞, Cmax, and trough concentrations at 24 hours.

The formulations studied were:

Table 5:

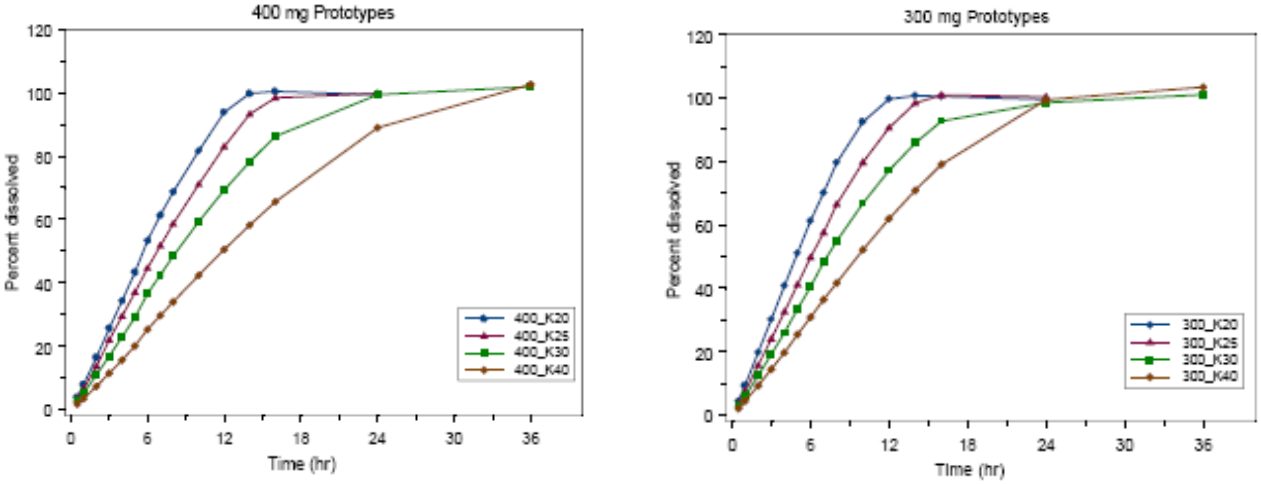
Release Rate	Dose (mg)	Composition
Fast	300	ECR 20%
	400	ECR 20%
Medium	300	KCR 20% KCR 25%
	400	KCR 20% KCR 25%
Slow	300	KCR 30% KCR 40%
	400	KCR 30% KCR 40%

The formulations were ranked by their dissolution rates in pH 6.8 phosphate buffer 2% sodium dodecyl (lauryl) sulfate at 37°C and 75 rpm (see Figure 2.2: 1). A Double Weibull model optimally fit the in vitro data.

$$y(t) = \text{int} + f1 * (F_{\text{inf}} - \text{int})(1 - e^{-\left[\frac{t}{MDT1}\right]^{b1}}) + (1 - f1) * (F_{\text{inf}} - \text{int})(1 - e^{-\left[\frac{t}{MDT2}\right]^{b2}})$$

where, Finf = amount released at time infinity; MDT = mean dissolution time; MDT1 and MDT2 = mean dissolution time for each Weibull; b1 and b2 = slope factors; int = y-intercept; f1 = weighting factor; Fmax = maximum y value; Tmax = time of maximum y value.

Figure 3:

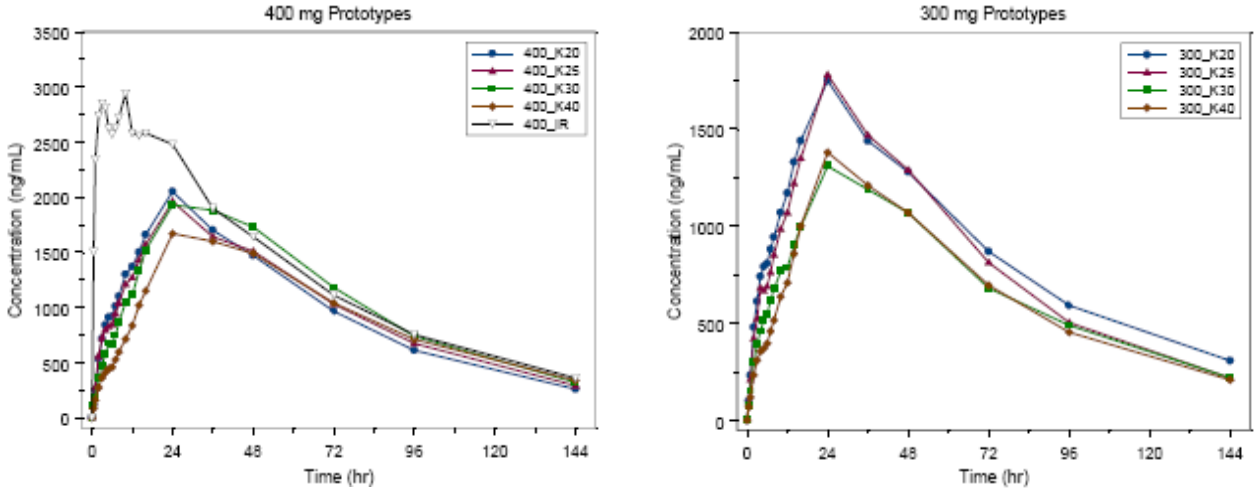


Mean in vitro dissolution profiles of nevirapine from 300 mg and 400 mg nevirapine extended release formulations

Results:

Bioavailabilities of nevirapine administered as single 300 mg and 400 mg dose extended release formulations were lower compared to a single dose of 2x200 mg nevirapine IR. These lower bioavailabilities were characterized by lower total plasma exposures, lower peak plasma nevirapine concentrations, and lower plasma nevirapine concentrations at 24 hours post-dose (see Figure below).

Figure 4:

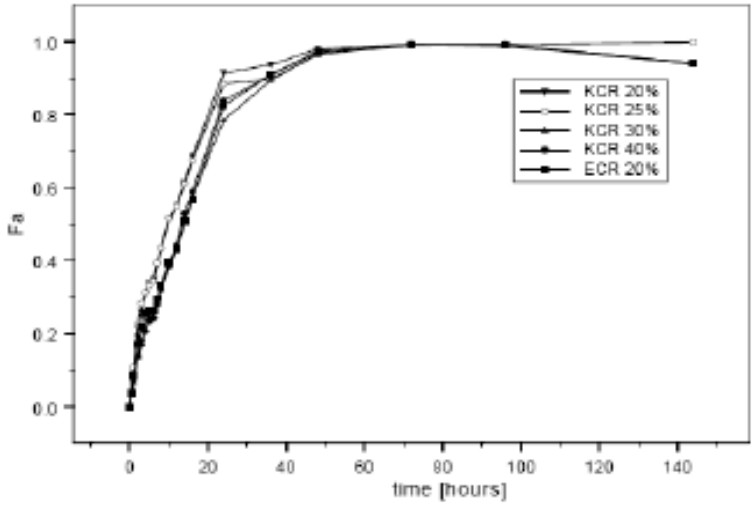


Mean in vivo concentration time profiles (0-144 h) of nevirapine following single oral administration of 300 mg and 400 mg nevirapine extended release formulations to healthy volunteers

Nevirapine ER KCR 20% data was evaluated using 1, 2, and 3 compartment models (corresponding to 2, 3, and 4 exponential terms, respectively) with first-order absorption. Based on model selection criteria, one compartment (2 exponential) model with 1/Ypred weighting appeared to best fit 400_K20 formulation concentration time data. Numerical deconvolution was performed to estimate the time

course of drug input with extended release formulations using UIR based on nevirapine ER 400 mg KCR 20% formulation.

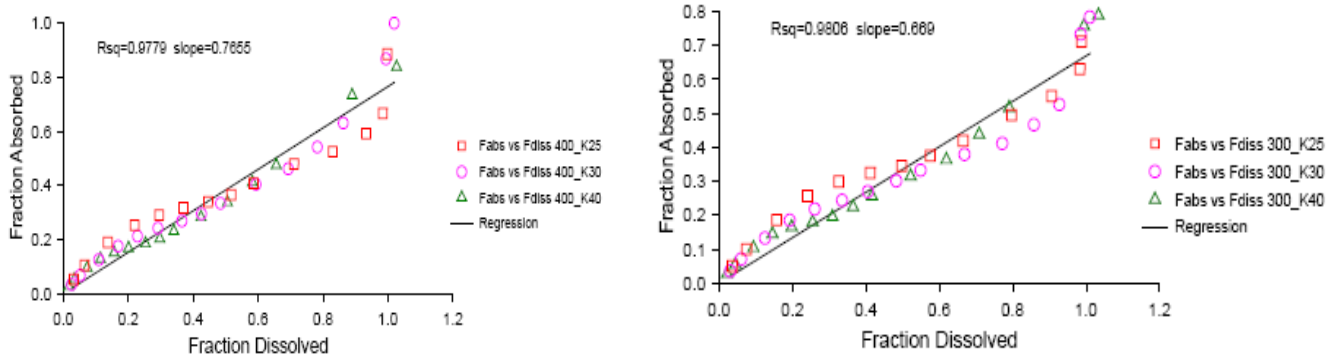
Figure 5:



Mean fractions of nevirapine absorbed (Fa) after oral administration of nevirapine XR 400 mg demonstrating linearity over the first 24 hand a maximum by 40 h

The resulting correlation is shown below:

Figure 6:



In vitro-in vivo correlations for 300 mg and 400 mg nevirapine extended release formulations

Validation results are shown in table below:

Table 6: Summary of internal validation parameters for nevirapine extended release 400 mg formulations

Parameter	Formulation	Predicted	Observed	%PE	Ratio
AUC_{0-tz} (ng·h/mL)	400 KCR 25%	146095	142582	2.5	1.02
	400 KCR 30%	145143	152905	-5.1	0.95
	400 KCR 40%	134460	134152	0.2	1.00
	Average	141899	143213	2.6	0.99
C_{max} (ng/mL)	400 KCR 25%	2169	1960	10.7	1.11
	400 KCR 30%	1933	1930	0.2	1.00
	400 KCR 40%	1748	1670	4.6	1.05
	Average	1950	1853	5.2	1.05

%PE = [(observed value – predicted value)/observed value]*100

Table 7: Summary of internal validation parameters for nevirapine extended release 400 mg formulations

Parameter	Formulation	Predicted	Observed	%PE	Ratio
AUC_{0-tz} (ng·h/mL)	400 KCR 25%	146095	142582	2.5	1.02
	400 KCR 30%	145143	152905	-5.1	0.95
	400 KCR 40%	134460	134152	0.2	1.00
	Average	141899	143213	2.6	0.99
C_{max} (ng/mL)	400 KCR 25%	2169	1960	10.7	1.11
	400 KCR 30%	1933	1930	0.2	1.00
	400 KCR 40%	1748	1670	4.6	1.05
	Average	1950	1853	5.2	1.05

%PE = [(observed value – predicted value)/observed value]*100

Conclusion:

The nevirapine prolonged release formulations showed a lower bioavailability after single dose administration compared to nevirapine IR 2x200 mg. Relative bioavailability, assessed by geometric mean test/reference ratios ranged between 62.1 and 87.1% for dose-normalized AUC0-∞, between 51.4 and 75.5% for dose normalized Cmax and between 62.6 and 92.8% for dose-normalized concentrations at 24 hours in relation to nevirapine IR 2x200 mg. A Level A in vitro/in vivo correlation was developed and validated for nevirapine extended release formulations providing robust predictions of in vivo profiles based on in vitro dissolution profiles.

Dissolution specifications based on the above in vitro-in vivo correlation.

- Bioequivalence

Trial 1100.1517:

An open-label, non-randomised, single-dose, parallel-group study of pharmacokinetic properties of 200 mg (2 x 100 mg tablets once daily) and 300 mg (3 x 100 mg tablets once daily) nevirapine extended release formulation compared to 200 mg nevirapine tablet as well as to 400 mg nevirapine extended release tablet following oral administration in healthy male volunteers

Objective:

To determine the pharmacokinetic properties of 200 mg (2 x 100 mg tablets once daily) and 300 mg (3 x 100 mg tablets once daily) nevirapine extended release formulation and to estimate relative

bioavailability of the nevirapine 100 mg XR tablet compared to 200 mg nevirapine IR tablet as well as to the 400 mg nevirapine extended release tablet.

Method:

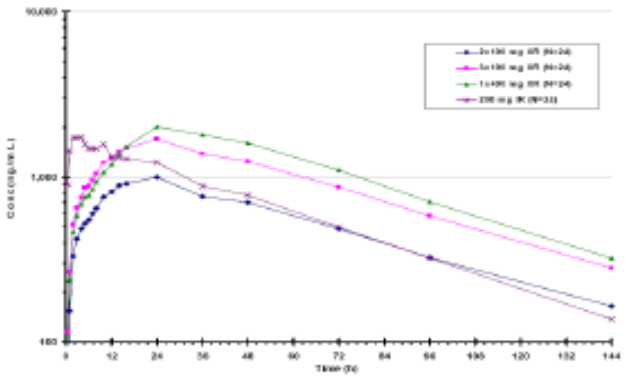
The study was performed as an open-label, non-randomised, single-dose, parallel-group trial. Each subject was treated only once. The treatments (n = 24 male subjects each) were 200 mg and 300 mg nevirapine extended release doses, given as 2 x 100 mg tablets or 3 x 100 mg tablets in the fasting state for test formulations, and one 400 mg nevirapine extended release tablet or one 200 mg nevirapine IR tablet in the fasting state for reference formulations. Blood was taken from a forearm vein at the following time points: before treatment, 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72, 96, and 144 hours after administration. Groups and treatments were as follows:

- Treatment Nevirapine XR 200: entered: 24, treated: 24, analysed (for primary endpoint): 24
- Treatment Nevirapine XR 300: entered: 24, treated: 24, analysed (for primary endpoint): 24
- Treatment Nevirapine XR 400: entered: 24, treated: 24, analysed (for primary endpoint): 24
- Treatment Nevirapine IR 200 (Viramune): entered: 24, treated: 24, analysed (for primary endpoint): 24

Results:

The paediatric 100 mg nevirapine prolonged release tablet strength administered either as two tablets (200 mg) or three tablets (300 mg) displayed prolonged absorption (median tmax ~24 h) compared to the nevirapine IR profile (median tmax 2 h). The absorption was more rapid for the 100 mg extended release tablet strength compared to the 400 mg prolonged release tablet strength (see Figure below).

Figure 7:



Geometric mean plasma nevirapine concentration-time profiles after single-dose oral administration of the same blend of extended release formulation at a different dose and tablet size

Comparative bioavailability analysis is shown in the following table:

Table 8: Relative bioavailability of NVP XR 200 mg and NVP XR 300 mg as compared to each of NVP XR 400 mg and NVP IR 200 mg (Viramune) with respect to Cmax,norm and AUC0-inf, norm

Comp. T/R	Reference 1 XR 400 mg			Reference 2 IR 200 mg		
Test formulation	Adj.mean Ratio (Test/ XR400mg)	90% conf. int. lower limit [%]	upper limit [%]	Adj.mean Ratio (Test/ IR200mg)	90% conf. int. lower limit [%]	upper limit [%]
XR 200mg						
$C_{max,norm}$	97.2	82.5	114.5	51.7	44.1	60.7
$AUC_{0-\infty,norm}$	95.1	78.2	115.5	83.0	68.2	100.9
XR 300mg						
$C_{max,norm}$	107.2	96.7	118.8	57.0	51.8	62.8
$AUC_{0-\infty,norm}$	112.9	100.3	127.1	98.5	87.3	111.2

Dose proportionality analysis is shown in the following table:

Table 9: Summary of statistical analyses of dose proportionality of NVP XR 200 mg and NVP XR 300 mg

Parameter	Type of analysis	N	point estimator for slope	95% CI Lower Limit	95% CI Upper Limit
C_{max}	Power model	48	1.242 (SD=0.2344)	0.77	1.71
	Paired comparison		1.242	−0.39	2.88
$AUC_{0-\infty}$	Power model	48	1.424 (SD=0.2842)	0.85	2.00
	Paired comparison		1.424	−0.56	3.41

Conclusions

In summary, the paediatric 100 mg XR tablet strength administered either as 2 tablets or 3 tablets showed very slow absorption (median tmax ~24 h) compared to the IR profile (median tmax 2 h). The absorption is slightly faster for the 100 mg XR tablet strength compared to the 400 mg XR tablet strength. No dose dumping was observed from the individual profiles and interindividual variability is similar to the IR tablet. Drug exposure (AUC0-∞ and Cmax) appear to be linear between the XR dose groups. Based on the dose normalized AUC0-∞, the relative bioavailability of the 100 mg XR tablet strength was 83% (2x100 mg XR) and 98.5% (3x100 mg XR) compared to IR tablet (1x200 mg), and was 95.1% (2x100 mg XR) and 112.9% (3x100 mg XR) compared to the 400 XR tablet strength.

Trial 1100.1531:

An open-label, randomised, single dose, parallel-group Phase I study to investigate the pharmacokinetic properties of 200 mg nevirapine extended release tablets when administered orally as 2x100 mg tablets or as 4x50 mg tablets in healthy male volunteers.

Objective:

To determine the bioequivalence of 200 mg nevirapine administered as 4 x 50 mg prolonged release tablets in a single dose to 200 mg nevirapine administered as 2 x 100 mg prolonged release tablets in a single dose based on the primary endpoints AUC0-∞ and Cmax.

Method:

The study was performed as an open-label, randomised, single-dose, parallel-group trial. Each subject was treated only once. The test treatment was 4 x 50 mg nevirapine prolonged release tablets while the reference treatment was 2 x 100 mg nevirapine prolonged release tablets. Both treatments were taken in the fasted state.

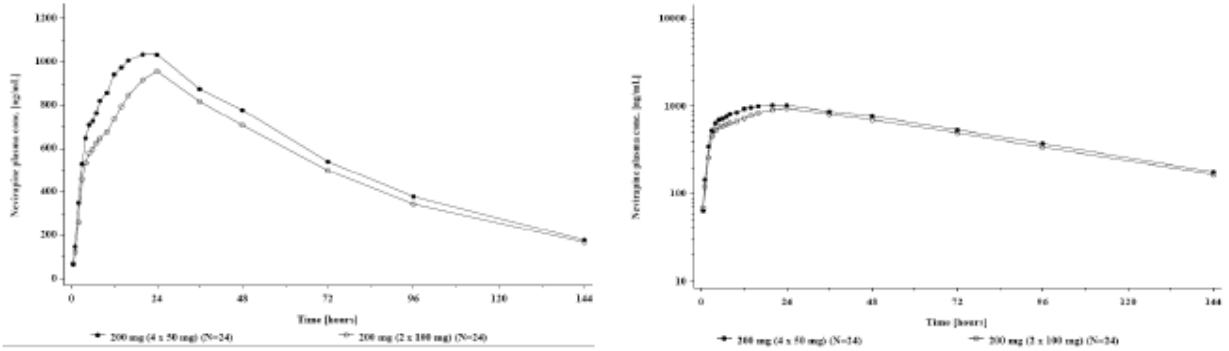
The inclusion criteria consisted of healthy males of 21 to 50 years of age. For quantitation of plasma nevirapine concentrations, blood was drawn before treatment and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48, 72, 96, and 144 h after dosing.

Results:

The plasma concentration-time profiles of nevirapine were similar in shape after single doses of 4 x 50 mg and 2 x 100 mg nevirapine extended release tablets. Absorption rates from both tablets were slow compared to historical nevirapine IR tablets, but the extent of absorption following the administration of the 50 mg tablet was 6 - 11% greater than that of the 100 mg tablet.

Elimination of nevirapine was monophasic after single doses of both 4 x 50 mg and 2 x 100 mg nevirapine extended release tablets and no treatment differences in the elimination phase were observed (Figure 2.4: 1). No dose dumping was observed in individual profiles, suggesting that the rate of absorption of nevirapine was consistent. Geometric mean plasma concentration-time profiles of nevirapine for both treatments are shown in Figure below.

Figure 8:



Geometric mean plasma nevirapine concentration-time profiles after a single dose of nevirapine extended release administered as either 4 x 50 mg or 2 x 100 mg tablets (left: linear; right: semilog)

Pharmacokinetic parameters and bioequivalence analysis are shown in the following two tables:

Table 10: Key pharmacokinetic parameters of nevirapine after a single dose of nevirapine extended release 50 and 100 mg tablets at a dose of 200 mg

	nevirapine extended release 4 x 50 mg n=24	nevirapine extended release 2 x 100 mg n=24
$AUC_{0-\infty}$ [ng·h/mL]	98,700 (30.8)	91,500 (35.8)
AUC_{0-tz} [ng·h/mL]	84,100 (26.5)	78,300 (33.5)
C_{max} [ng/mL]	1,130 (22.3)	1,080 (29.5)
t_{max} [h]	18.1 (34.0)	18.1 (42.0)
k_a [h^{-1}]	0.150 (73.3)	0.170 (89.3)
λ_z [h^{-1}]	0.0154 (23.4)	0.0152 (16.0)
MRT_{po} [h]	76.4 (19.1)	76.5 (15.0)
CL/F [mL/min]	37.0 (31.6)	43.1 (50.8)
V_z/F [mL/min]	147 (32.8)	172 (50.5)
$t_{1/2}$ [h]	47.1 (21.4)	46.8 (17.6)

Data are presented as mean (% CV).

Table 11: Adjusted-by-treatment geometric means and relative bioavailability for nevirapine extended release 4 x 50 mg tablets as compared to nevirapine extended release 2 x 100 mg tablets with respect to Cmax, AUC0-∞, and AUC0-tz

	Adjusted gMean				2-sided 90% confidence intervals	
	NVP XR 4 x 50 mg (Test) n=24	NVP XR 2 x 100 mg (Reference) n=24	Ratio Test/Reference [%]	Intra-individual gCV [%]	Lower limit (%)	Upper limit (%)
C_{max} [ng/mL]	1097.090	1028.221	106.7	29.5	92.8	122.7
$AUC_{0-\infty}$ [µg·h/mL]	94.383	84.938	111.1	38.0	93.1	132.8
AUC_{0-tz} [µg·h/mL]	81.152	73.210	110.9	35.5	93.9	131.0

Conclusion:

As with the paediatric 100 mg nevirapine prolonged release tablet strength (administered as two tablets) single dose plasma nevirapine concentration-time profiles, the smaller paediatric 50 mg nevirapine prolonged release tablet strength administered as four tablets showed prolonged absorption (median tmax ~18 h) compared to historical nevirapine IR profiles (median tmax ~2 h). The 50 mg nevirapine prolonged release strength (a round 7 mm tablet) is the same common formulation blend (Methocel Type 2208, 4000 cPs, KCR 25%) as the 100 mg nevirapine prolonged release tablet (a round 9 mm tablet). Dividing the 200 mg total dose into four 50 mg units rather than two 100 mg units produced a greater overall absorption, but with comparable drug release rates. Although criteria for bioequivalence was not fulfilled, the higher exposure observed with the 4x50 mg nevirapine XR tablets compensates for the lower bioavailability observed with the 2x100 mg nevirapine XR tablets compared with 200 mg nevirapine IR (see parallel group trial 1100.1517).

The applicant summarises the results from these two trials (1100.1531 & 1100.1517) as follows:

Table 12: Comparisons of mean (%CV) pharmacokinetic parameters across studies for the two pediatric strengths (each parameter is the compilation of 24 individuals in a parallel group design at a 200 mg dose)

Parameter	1100.1531		1100.1517	
Treatment	4 x 50 mg XR	2 x 100 mg XR	2 x 100 mg XR	200 mg IR
$AUC_{0\rightarrow\infty}$ (ng•h/mL)	98,700 (31)	91,500 (36)	91,800 (33)	105,000 (28)
C_{max} (ng/mL)	1,130 (22)	1,080 (30)	1,100 (29)	2,030 (19)
t_{max} (h)	18.1 (34)	18.1 (42)	19.6 (34)	2.7 (74)
$t_{1/2}$ (h)	47.1 (21)	46.8 (17)	47.7 (24)	41.5 (25)

The observed pharmacokinetic difference between the 4x50 mg and 2x100 mg nevirapine XR tablets is not considered clinically relevant, and the 50 mg nevirapine XR tablet can be used as an alternative in children not able to swallow the slightly larger 100 mg nevirapine XR tablet.

- **Influence of food**

Study 1100.1489:

Steady state relative bioavailability and food effect of two different nevirapine prolonged release prototype formulations compared to steady state 400 mg of Viramune (200 mg BID), in HIV-1 infected subjects, an open label, non randomised, multidose and multistage parallel group study

Objective:

To establish the steady state pharmacokinetic profiles and relative bioavailability of 2 different nevirapine XR formulations (KCR 20 and 25%), in two dose strengths (300 and 400 mg), under fasting and fed conditions, in comparison to nevirapine IR

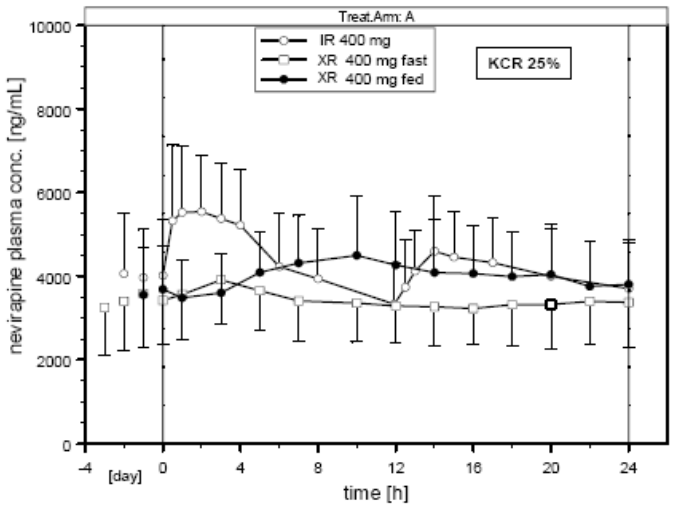
Method:

This was an international, open label, multistage, parallel group, crossover study. HIV-1 infected patients treated for >12 weeks with nevirapine IR (Viramune) 200 mg BID without protease inhibitors. After obtaining intensive PK plasma samples for nevirapine IR over a 24 hour period on study Day 3, patients were switched to two different formulations of nevirapine XR 400 mg QD (Group A: KCR 25%, Group B: KCR 20%) or 300 mg QD (Group C: KCR 25%, Group D: KCR 20%) on Day 4 for 19 days to evaluate relative bioavailability compared to nevirapine IR. Intensive PK plasma samples for XR administrations were collected over a 24 h period on study Day 18 without food and on Day 22 with food. Background ARV medication was maintained throughout the study.

Trough plasma samples were also collected for several days preceding the intensive PK sampling days. Plasma nevirapine concentrations were determined by a validated HPLC-MS/MS assay with a lower limit of quantitation of 25 ng/mL; while plasma concentrations of 5 metabolites were determined by a separate validated HPLC-MS/MS assay method.

Results

Figure 9:



Mean (SD) nevirapine plasma concentration-time profiles after administration of nevirapine XR KCR 25% 400 mg QD in fasted and fed state versus nevirapine IR 200 mg BID in fasted state

For all nevirapine XR formulations (300 mg and 400 mg QD), slightly lower mean exposures (Cmax,ss, AUC0-24,ss) were observed compared to the nevirapine IR 200 mg BID formulation. Mean (SD) plasma concentration-time profiles of nevirapine at steady-state after repeated once-daily oral administration of the KCR 25% nevirapine XR 400 mg formulation given with and without food compared with those of nevirapine IR 400 mg/day are shown in Figure above. As expected, nevirapine IR exhibited two peak/trough cycles over the 24-hour period, with the morning profile slightly higher than the evening profile.

Mean plasma concentrations of nevirapine moderately increased when the XR formulations were administered with a high fat breakfast compared to administration in the fasted state, which was consistent for all four prototypes. The plasma concentration-time profile for the finally selected nevirapine XR KCR 25% formulation in the fed state was slightly higher than in the fasted state, but still below the IR's two peak/trough cycles for most of the time points over the 24-hour period (Figure above). No dose dumping was observed for any of the nevirapine XR individual profiles with and without food co-administration.

Plasma nevirapine concentrations increased with dose from 300 mg to 400 mg for both prototype nevirapine XR formulations. Nevirapine pharmacokinetics parameters for all treatment groups are listed in Tables below.

Table 13: Multiple dose PK parameters of nevirapine XR tablets for 400 mg XR treatment groups in HIV-1 patients

Parameter	Unit		Treatment A NVP XR 400 mg KCR 25%			Treatment B NVP XR 400 mg KCR 20%		
			IR (N=24)	XR fasted (N=24)	XR fed (N=24)	IR (N=24)	XR fasted (N=23)	XR fed (N=23)
$t_{max,ss}$	[h]	Mean	1.74	6.71	9.57	1.97	8.63	7.67
		(CV[%])	(57.3)	(120)	(56.0)	(55.9)	(97.7)	(54.9)
		gMean#	1.47	4.14	6.08	1.62	2.91	6.75
$C_{max,ss}$	[ng/mL]	Mean	5,950	4,140	5,010	7,340	4,850	6,230
		(CV[%])	(26.8)	(22.4)	(25.6)	(33.9)	(42.3)	(31.8)
		gMean	5,750	4,040	4,850	7,000	4,470	5,980
$C_{min,ss}$	[ng/mL]	Mean	3,240	2,920	3,150	4,500	3,600	4,010
		(CV[%])	(30.9)	(32.3)	(27.7)	(40.0)	(49.0)	(43.8)
		gMean	3,090	2,770	3,030	4,220	3,190	3,680
$C_{max,ss}$/ $C_{min,ss}$ Ratio		Mean	1.87	1.48	1.62	1.67	1.42	1.67
		(CV[%])	(12.9)	(16.4)	(16.6)	(12.5)	(16.6)	(25.7)
		gMean	1.86	1.46	1.60	1.66	1.40	1.62
C_{avg}	[ng/mL]	Mean	4,280	3,420	4,030	5,690	4,220	5,140
		(CV[%])	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	4,140	3,290	3,900	5,390	3,860	4,880
$AUC_{0-24,ss}$	[ng·h/mL]	Mean	103,000	82,000	96,700	137,000	101,000	123,000
		(CV[%])	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	99,400	79,000	93,700	129,000	92,700	117,000
PTF*	[%]	Mean	64.4	38.6	46.7	51.8	32.7	46.5
		(CV[%])	(21.5)	(41.8)	(34.5)	(27.0)	(44.8)	(43.8)
		gMean	63.0	35.2	44.3	50.1	29.7	42.3

*Peak-to-trough fluctuation; #gMean: geometric mean

A table summarising the above results for treatment A is presented below

Table 14: Steady state PK parameters of nevirapine IR (200 mg BID) and nevirapine XR (KCR 25%) tablets (400 mg QD), within-group comparison (Treatment A)

PK Parameter		$t_{max,ss}$ [h]	$C_{max,ss}$ [ng/mL]	$C_{min,ss}$ [ng/mL]	$C_{max,,ss}/C_{min,,ss}$ ratio	$AUC_{0-24,ss}$ [ng·h/mL]
NVP IR fasted	Mean	1.74	5,950	3,240	1.87	103,000
(N=24)	CV [%]	**57.3**	**26.8**	**30.9**	**12.9**	**26.2**
NVP XR fasted	Mean	6.71	4140	2920	1.48	82,000
(N=24)	CV [%]	**120**	**22.4**	**32.3**	**16.4**	**27.1**
NVP XR fed	Mean	9.57	5,010	3,150	1.62	96,700
(N=24)	CV [%]	**56.0**	**25.6**	**27.7**	**16.6**	**25.0**

*PK parameters obtained over the 24 hour period with a morning dose and an evening dose

Table 15: Multiple dose PK parameters of nevirapine XR tablets for 300 mg XR treatment groups in HIV-1 patients

Parameter	Unit		Treatment C NVP XR 300 mg KCR 25%			Treatment D NVP XR 300 mg KCR 20%		
			IR (N=21)	XR fasted (N=21)	XR fed (N=21)	IR (N=23)	XR fasted (N=23)	XR fed (N=23)
$t_{max,ss}$	[h]	Mean	1.89	7.07	9.51	1.94	7.96	7.77
		(CV[%])	(63.4)	(74.4)	(51.4)	(54.1)	(78.3)	(44.2)
		gMean*	1.55	4.02	8.48	1.43	6.01	7.17
$C_{max,ss}$	[ng/mL]	Mean	6,090	3,580	4,270	6,330	3,560	4,600
		(CV[%])	(22.1)	(30.4)	(47.3)	(25.9)	(25.2)	(29.6)
		gMean	5,960	3,450	3,890	6,150	3,460	4,430
$C_{min,ss}$	[ng/mL]	Mean	3,250	2,370	2,640	3,650	2,300	2,670
		(CV[%])	(35.4)	(28.1)	(53.8)	(34.5)	(33.0)	(36.5)
		gMean	3,050	2,290	2,300	3,480	2,180	2,520
$C_{max,ss}$/ $C_{min,ss}$ Ratio		Mean	1.99	1.52	1.75	1.79	1.60	1.79
		(CV[%])	(21.6)	(14.2)	(29.8)	(15.8)	(16.0)	(18.6)
		gMean	1.95	1.51	1.69	1.77	1.59	1.76
C_{avg}	[ng/mL]	Mean	4,300	2,920	3,420	4,700	2,940	3,590
		(CV[%])	(25.1)	(29.3)	(48.0)	(29.6)	(25.9)	(28.7)
		gMean	4,180	2,820	3,100	4,530	2,840	3,460
$AUC_{0-24,ss}$	[ng·h/mL]	Mean	103,000	70,100	82,100	113,000	70,600	86,100
		(CV[%])	(25.1)	(29.3)	(48.0)	(29.6)	(25.9)	(28.7)
		gMean	100,000	67,700	74,500	109,000	68,200	83,000
PTF*	[%]	Mean	69.3	41.3	50.8	59.1	44.5	55.2
		(CV[%])	(27.4)	(31.7)	(42.7)	(27.6)	(28.9)	(30.7)
		gMean	67.0	39.3	46.3	56.6	42.7	52.5

*Peak-to-trough fluctuation; #gMean: geometric mean

Compared with nevirapine IR, both nevirapine XR 400 mg formulations (Groups A and B) resulted in longer tmax,ss (Table above) and lower Cmax.ss; whereas Cmin,ss was similar in Group A (gMean XR/IR ratio of Cmin,ss: 89.6%) and lower in Group B (gMean XR/IR ratio of Cmin,ss: 75.1%).

Table 16: Relative bioavailability of prototype nevirapine XR formulations administered QD in fasted conditions versus nevirapine IR 200 mg BID in fasted conditions

Parameter [Unit] Formulation	N#	XR Adjusted gMean	IR Adjusted gMean	Adjusted gMean Ratio (Test:Ref) [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]
$AUC_{0-24,ss}$ [ng•h/mL]						
400 mg KCR 25% (A)	24/24	79,000	99,400	**79.5**	73.0	86.7
400 mg KCR 20% (B)	23/23	92,700	129,000	**71.0**	63.3	79.7
300 mg KCR 25% (C)	20/20	66,700	100,000	**90.3***	80.4	101.4
300 mg KCR 20% (D)	23/23	68,200	109,000	**83.7***	77.9	89.9
$C_{max,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	4,040	5,750	**70.2**	64.6	76.3
400 mg KCR 20% (B)	23/23	4,470	7,000	**63.7**	56.8	71.4
300 mg KCR 25% (C)	20/20	3450	5690	**77.0***	68.3	86.7
300 mg KCR 20% (D)	23/23	3460	6150	**74.9***	69.1	81.2
$C_{min,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	2,770	3,090	**89.6**	80.6	99.6
400 mg KCR 20% (B)	23/23	3,190	4,220	**75.1**	65.1	86.5
300 mg KCR 25% (C)	20/20	2,290	3,050	**99.4***	84.2	117.4
300 mg KCR 20% (D)	23/23	2,180	3,480	**83.5***	77.0	90.5

N of test / N of reference (ref)
* Ratios for 300 mg dose groups are presented based on dose-adjusted values

Relative bioavailability (Table above) compared with nevirapine IR (based on geometric mean [gMean] XR/IR ratios of AUC0-24,ss) within the same treatment group was 79.5% for KCR 25% 400 mg QD (Group A) , 71.0% for KCR 20% 400 mg QD (Group B), 90.3% for KCR 25% 300 mg QD (Group C) and 83.7% for KCR 20% 300 mg QD (Group D) (values for the 300 mg groups are based on dose-adjusted values).

Table 17: Effect of a high fat breakfast on nevirapine absorption of XR formulations administered QD in fed versus fasted conditions

Parameter, [Unit] Formulation	N#	XR fed Adjusted gMean	XR fasted Adjusted gMean	Adjusted gMean Ratio (Test:Ref) [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]
$AUC_{0-24,ss}$ [ng•h/mL]						
400 mg KCR 25% (A)	24/24	93,700	79,000	**118.5**	108.8	129.2
400 mg KCR 20% (B)	23/23	117,000	92,700	**126.3**	112.6	141.7
300 mg KCR 25% (C)	20/20	74,500	66,700	**108.4**	96.5	121.8
300 mg KCR 20% (D)	23/23	83,000	68,200	**121.6**	113.2	130.6
$C_{max,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	4,850	4,040	**120.2**	110.6	130.7
400 mg KCR 20% (B)	23/23	5,980	4,470	**133.8**	119.4	150.0
300 mg KCR 25% (C)	20/20	3,890	3,450	**111.4**	98.9	125.4
300 mg KCR 20% (D)	22/23	4,430	3,460	**129.3**	119.1	140.3
$C_{min,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	3,030	2,770	**109.6**	98.6	121.8
400 mg KCR 20% (B)	23/23	3,680	3,190	**115.3**	100.0	132.9
300 mg KCR 25% (C)	20/20	2,300	2,290	**99.8**	84.5	117.8
300 mg KCR 20% (D)	23/23	2,520	2,180	**115.5**	106.6	125.3

N of test / N of reference (ref)

Table 18: Relative bioavailability of nevirapine XR formulations administered QD in fed state versus nevirapine IR 200 mg BID in fasted state

Parameter, Unit Formulation	N#	XR fed	IR fasted	Adjusted gMean Ratio (Test:Ref) [%]	90% Confidence interval	
		Adjusted gMean	Adjusted gMean		Lower limit [%]	Upper limit [%]
$AUC_{0\text{-}24,ss}$ [ng•h/mL]						
400 mg KCR 25% (A)	24/24	93,700	99,400	**94.3**	86.5	102.8
400 mg KCR 20% (B)	23/23	117,000	129,000	**89.7**	80.0	100.6
300 mg KCR 25% (C)	20/20	74,500	100,000	**97.9***	87.1	110.0
300 mg KCR 20% (D)	23/23	83,000	109,000	**101.7***	94.7	109.3
$C_{max,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	4,850	5,750	**84.4**	77.6	91.7
400 mg KCR 20% (B)	23/23	5,980	7,000	**85.2**	76.1	95.5
300 mg KCR 25% (C)	20/20	3,890	5,960	**85.7***	76.1	96.5
300 mg KCR 20% (D)	22/23	4,430	6,150	**96.8***	89.2	105.1
$C_{min,ss}$ [ng/mL]						
400 mg KCR 25% (A)	24/24	3,030	3,090	**98.2**	88.4	109.1
400 mg KCR 20% (B)	23/23	3,680	4,220	**86.6**	75.1	99.8
300 mg KCR 25% (C)	20/20	2,300	3,050	**99.2***	84.0	117.1
300 mg KCR 20% (D)	23/23	2,520	3,480	**96.5***	89.0	104.6

N of test / N of reference (ref)

* Ratios for 300 mg dose groups are presented based on dose-adjusted values

The mean plasma concentration ratios of three nevirapine metabolites appeared similar after oral administration of nevirapine XR and IR formulations. In addition, administration of nevirapine XR with food did not show any effects on nevirapine metabolite ratios compared with administration of the drug product in the fasted state (see Table below). Note that only three metabolites are summarized since 2-hydroxynevirapine and 8-hydroxynevirapine plasma concentrations were below limit of quantitation for both nevirapine XR and nevirapine IR.

Table 19: Plasma concentration ratios of metabolite to nevirapine for nevirapine IR (200 mg BID) and XR (KCR 25%) tablets (400 mg QD) in the same group of HIV-1 patients (Treatment A)

		NVP IR		NVP XR fasted		NVP XR fed	
Metabolite	Time [h]	0*	24*	0*	24*	0*	24*
12-Hydroxynevirapine	Mean	0.0555	0.0526	0.0479	0.0478	0.0467	0.0472
	CV [%]	28.6	20.8	25.3	22.9	30.6	20.0
	gMean	0.0532	0.0514	0.0465	0.0465	0.0448	0.0463
3-Hydroxynevirapine	Mean	0.0139	0.0148	0.0123	0.0129	0.0133	0.0130
	CV [%]	39.1	31.4	26.4	29.6	42.9	34.7
	gMean	0.0132	0.0142	0.0119	0.0124	0.0125	0.0123
4-Carboxynevirapine	Mean	0.00321	0.00272	0.00193	0.00224	0.00239	0.00199
	CV [%]	67.1	70.0	99.5	90.7	88.0	96.7
	gMean	0.00111	0.000747	0.000237	0.000316	0.0004	0.000243

Note: 2-Hydroxynevirapine and 8-hydroxynevirapine are not shown since their plasma concentrations were below limit of quantitation for nevirapine XR and nevirapine IR.

*Nevirapine metabolites samples were collected before (0 h) and 24 h after drug administration on Day 3 for IR, on Day 18 for nevirapine XR fasted, and on Day 22 for nevirapine XR fed.

Conclusions

Administration of nevirapine from both XR formulations 400 mg QD resulted in extended absorption and moderate reductions in peak levels at steady state with minimal reductions in Cmin,ss values compared to nevirapine IR 200 mg BID. When nevirapine XR formulations were administered with food, the relative bioavailability of nevirapine tended to be slightly higher than in the fasted state, close to exposures observed with the nevirapine IR formulation. However, the extent of the increase was not clinically relevant and was not sufficient to warrant a recommendation with regard to food intake. Based on these results, the KCR 25% 400 mg formulation exhibited better relative bioavailability and less variability than the KCR 20% formulation and was selected as the final XR tablet formulation for the Phase III studies.

Dose proportionality and time dependencies

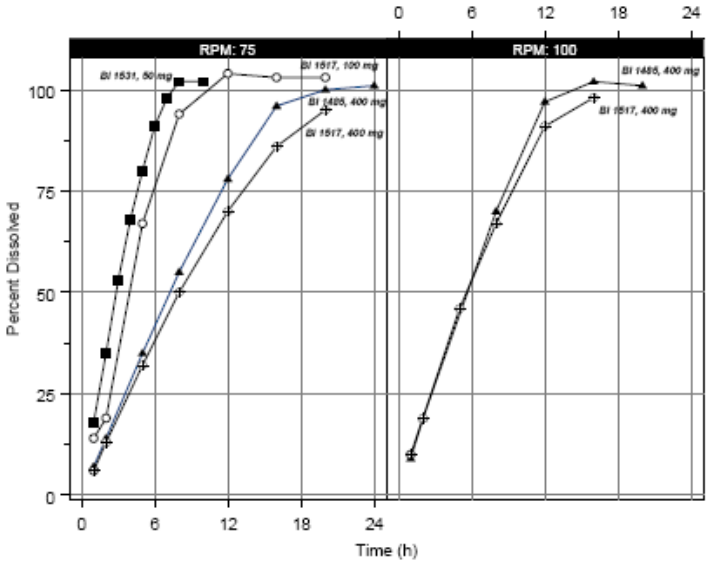
- Dose proportionality

Dose proportionality was demonstrated on the basis of trial 1100-1517 discussed under Bioequivalence.

The 100 mg paediatric nevirapine XR tablets are round, approximately 9 mm diameter, to facilitate dosing requirements in children who are able to reliably swallow such tablets. These tablets were based on the same formulation blend (KCR 25%) as the 400 mg adult nevirapine XR tablet with oval, biconvex dimensions of 9.3 x 19.1 mm. Therefore, because bioavailability is comparable to the 400 mg strength, the in vitro dissolution for the 100 mg paediatric nevirapine XR tablet strength correlates with the in vivo performance in a manner consistent with the 400 mg adult nevirapine XR tablet.

The 50 mg nevirapine prolonged release strength (a round 7 mm tablet) is also the same common formulation blend (Methocel Type 2208, 4000 cPs, KCR 25%) as the 100 mg nevirapine extended release tablet (a round 9 mm tablet) and the 400 mg nevirapine extended release tablet (oval, dimensions of 9.3 x 19.1 mm). The smaller 50 mg tablet unit produced a 7 - 11% greater overall dose-normalized exposure compared with the 100 mg tablet units, but with a comparable drug release rate. The in vivo drug release rates were consistent with the in vitro drug release dissolution profiles (Figure below).

Figure 10:



In vitro dissolution of nevirapine XR tablets prior to the in vivo bioequivalence trials of 1100.1485, 1517, and 1531

- **Time dependency**

Single dose bioavailability studies were conducted in healthy male volunteers. Nevirapine terminal elimination half life in plasma following a single dose administration was approximately 40 to 45 h. The half life did not differ between nevirapine XR and nevirapine IR formulations.

Nevirapine is an enzyme inducer and can induce its own CYP3A and CYP2B6 mediated metabolism, which leads to an approximately 1.5- to 2-fold increase in the apparent oral clearance (CL/F) of nevirapine as treatment continues from the first dose to steady state. Auto-induction also results in a corresponding decrease in the terminal half life of nevirapine in plasma to approximately 25-30 hours following multiple dosing with 200-400 mg/day. In the multiple dose study with intensive PK sampling (1100.1489) in HIV-1 patients, half life was not obtainable because no washout period could be included. Other available steady state PK parameters from this study compared with their corresponding single dose PK parameters (for the same XR KCR 25% formulation) obtained in the bioavailability study (1100.1485) are summarized in Table below.

Table 20: Across study comparisons between single dose (SD) and multiple dose (MD) pharmacokinetic parameters (gMean) of nevirapine IR and nevirapine XR (KCR 25%) tablets

Treatment	Study	1100.1485	Treatment	Study	1100.1485
NVP XR SD	Parameter	400 mg SD N = 17	NVP IR SD	Parameter	400 mg SD N = 17
	$AUC_{0-\infty}$ [ng·h/mL]	155,000		$AUC_{0-\infty}$ [ng·h/mL]	210,000
	$C_{max,1}$ [ng/mL]	1,970		C_{max} [ng/mL]	3,130
	$C_{min,1}$ [ng/mL]	1,840		$C_{min,1}$ [ng/mL]	1,230
	$AUC_{0-24,1}$ [ng·h/mL]	30,000		$AUC_{0-24,1}$ [ng·h/mL]	31,000
	CL/F [mL/min]	43.1		CL/F [mL/min]	31.7
	$t_{1/2}$ [h]	40.0		$t_{1/2}$ [h]	42.7
Treatment	**Study**	**1100.1489**	**Treatment**	**Study**	**1100.1489**
NVP XR MD	Parameter	400 mg QD N = 24	NVP IR MD	Parameter	200 mg BID N = 24
	$AUC_{0-24,ss}$ [ng·h/mL]	82,000		$AUC_{0-24,ss}$ [ng·h/mL]	99,400
	$C_{max,ss}$ [ng/mL]	4,140		$C_{max,ss}$ [ng/mL]	5,750
	$C_{min,ss}$ [ng/mL]	3,190		$C_{min,ss}$ [ng/mL]	3,090
	CL/F_{ss} [mL/min]	84.3		CL/F_{ss} [mL/min]	59.1
NVP XR MD/SD Ratio	$AUC_{0-24,ss}/AUC_{0-\infty}$	0.53	**NVP IR MD/SD Ratio**	$AUC_{0-24,ss}/AUC_{0-\infty}$	0.47
	$CL/F_{ss}/CL/F$	1.96		$CL/F_{ss}/CL/F$	1.86
	$C_{max,ss}/C_{max,1}$	2.10		$C_{max,ss}/C_{max,1}$	1.84
	$C_{min,ss}/C_{min,1}$	1.73		$C_{min,ss}/C_{min,1}$	2.51
	$AUC_{0-24,ss}/AUC_{0-24,1}$	2.73		$AUC_{0-24,ss}/AUC_{0-24,1}$	3.21

Since steady state half-life is still relatively long (25-30 h), accumulation of plasma concentrations would be expected for nevirapine independent of formulation as shown in Table above. Accumulation ratios for pharmacokinetic parameters over a constant dosing interval were estimated as Cmax,ss/Cmax,1, Cmin,ss/Cmin,1 and AUCт,ss/AUC0-24,1, where 1 denotes the single (or first) dose.

There is an approximately 2-fold accumulation for Cmax and Cmin, and approximately 3-fold accumulation in AUC at steady state for both nevirapine XR and IR tablets.

The combination of nevirapine's relatively long steady state half life and the BID dosing of the IR tablet results in a small peak-to-trough ratio of 1.9. Development of the nevirapine XR once-daily formulation results in a further reduction of the peak-to-trough ratio to 1.5, attaining more stable plasma concentrations despite the larger dosing interval (24 h instead of 12 h).

Intra- and inter-individual variability

From studies presented in the bioavailability/bioequivalence sections, the overall variability of the 400 mg prolonged release nevirapine dosage formulations were 20–47% for rate and extent of absorption indicating that some absorption occurs in the colonic regions of the gastrointestinal tract despite the presence of a high pH environment. Additionally, the relative systemic bioavailability is lower for the prolonged release formulations compared to the commercial tablet standard. For the 400 mg prolonged release nevirapine tablet intended for marketing (KCR 25%), the variability was 29% (AUC) to 37% (C24) with a relative bioavailability of approximately 70%.

Table 21: Study 1100.1486: Steady state PK sub-study parameters of nevirapine XR 400 mg QD and nevirapine IR 200 mg BID on Day 28 under fasted conditions

PK Parameter		$t_{max,ss}$ [h]	$C_{max,ss}$ [ng/mL]	$C_{min,ss}$ [ng/mL]	$AUC_{0-24,ss}$ [ng·h/mL]	CL/F_{ss} [mL/min]
NVP XR 400 mg QD	Mean	6.51	3,940	2,760	79,200	94.6
N = 24	CV [%]	**104**	**29.1**	**34.3**	**29.5**	**40.6**
NVP IR 200 mg BID	Mean	2.08	5,660	3,350	103,000	72.8
N = 25	CV [%]	**43.4**	**26.5**	**33.8**	**29.9**	**49.7**

Table 22: Study 1100.1518: Steady state PK substudy parameters of nevirapine XR QD and nevirapine IR BID under fasted conditions

PK Parameter		$t_{max,ss}$ [h]	$C_{max,ss}$ [ng/mL]	$C_{min,ss}$ [ng/mL]	$AUC_{\tau,ss}$ [a] [ng·h/mL]	CL/F_{ss} [b] [mL/min]
NVP XR 200 mg QD	Mean	6.34	5,810	3,320	106,000	35.7
N = 23	CV [%]	**104**	**42.7**	**44.2**	**41.0**	**34.0**
NVP IR (175-249 mg/day)	Mean	2.46	7,820	3,750	63,800	32.0
N = 22	CV [%]	**57.9**	**61.0**	**55.1**	**50.3**	**38.9**
NVP 300 mg QD	Mean	7.28	8,920	4,850	160,000	38.2
N = 11	CV [%]	**121**	**50.0**	**61.2**	**51.9**	**42.6**
NVP IR (250-349 mg/day)	Mean	2.49	6,890	3,820	61,400	39.0
N = 12	CV [%]	**50.4**	**33.4**	**37.7**	**36.9**	**29.9**
NVP 400 mg QD	Mean	5.73	6,460	3,880	122,000	72.5
N = 11	CV [%]	**129**	**42.3**	**47.6**	**45.1**	**68.3**
NVP IR (350-400 mg/day)	Mean	4.41	8,460	5,310	78,800	46.8
N = 15	CV [%]	**94.2**	**44.1**	**40.1**	**40.7**	**34.0**

[a] Doing interval τ=24 for XR and τ=12 for IR; [b] Unit expressed in mL/min

Table 23: Study 1100.1489: Steady state intra-individual variability of nevirapine in HIV-1 patients receiving XR 400 mg QD (KCR 25%) under fed and fasted conditions, and IR 200 mg BID under fasted conditions

PK Parameter [unit]	NVP XR 400 mg QD fed, adjusted gMean	NVP XR 400 mg QD fasted, adjusted gMean	NVP IR 200 mg BID fasted, adjusted gMean	Intra-individual gCV* [%]
$AUC_{\tau,ss}$ [ng•h/mL]	93,700	79,000	99,400	**17.9**
$C_{max,ss}$ [ng/mL]	4,850	4,040	5,750	**17.4**
$C_{min,ss}$ [ng/mL]	3,030	2,770	3,090	**22.0**

Table 24: Study 1100.1518: Steady state intra-individual variability of nevirapine in HIV-1 paediatric patients receiving XR QD under fed and fasted conditions, and IR BID under fasted conditions

PK Parameter [unit]	NVP XR N	NVP XR Adjusted gMean	NVP IR N	NVP IR Adjusted gMean	Intra-individual gCV* (%)
All available patients – all doses					
$C_{pre,ss}$ [ng/mL]	74	4,149	78	4,518	34.5
Intensive PK subgroup – All doses					
$AUC_{\tau,ss}$ [µg·h/mL][a]	45	113	49	124	26.8
$C_{max,ss}$ [ng/mL]	45	6,055	49	7,056	36.2
$C_{min,ss}$ [ng/mL]	45	3,474	49	3,814	29.5

*Geometric coefficient of variation
[a]Adjusted for NVP IR as two 12 h dosing intervals
Note: Both XR and IR administered after a fasting period of at least 4 hours

Pharmacokinetics in target population

Study 1100.1486:

A randomised, 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®, including a PK Sub-study at week 4.

Objective:

Secondary objectives were to evaluate safety and pharmacokinetics of nevirapine XR compared to nevirapine IR.

Methods:

A pharmacokinetic sub-study was also included in a total of 49 patients who had intensive PK blood sample collection over 24 hours at Week 4 (Day 28), i.e. 2 weeks after randomization. Plasma nevirapine concentrations were determined by a validated HPLC-MS/MS assay with a lower limit of

quantitation of 25 ng/mL. PK results were compared by treatment, and summarised by gender, race and study region, and baseline viral load stratum.

PK Results:

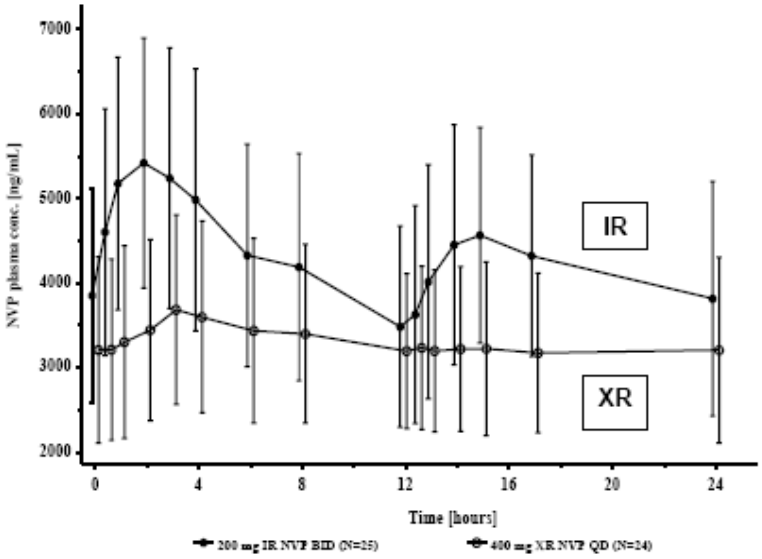
From the PK sub-study at Week 4, the relative bioavailability of nevirapine XR based on the geometric mean ratio (Table below) was 76.7% for AUC0-24,ss, 82.7% for Cmin,ss, and 68.9% for Cmax,ss. A lower Cmax,ss is expected and desirable for nevirapine XR by formulation design.

Table 25: Relative bioavailability of PK sub study parameters and nevirapine trough concentrations

Parameter	Test: NVP XR 400 mg QD		Reference: NVP IR 200 mg BID		Adjusted gMean Ratio (Test/ Reference)	90% Confidence Interval	
	N	Adjusted gMean	N	Adjusted gMean	%	Lower limit (%)	Upper limit (%)
PK Sub-study							
$AUC_{0\text{-}24,ss}$ [ng · h/mL]	24	75,323	25	96,176	**76.72**	65.14	90.37
$C_{min,ss}$ [ng/mL]	24	2,581	25	3,121	**82.69**	67.52	101.27
$C_{max,ss}$ [ng/mL]	24	3,767	25	5,464	**68.94**	59.79	79.48
All Patients							
Week 48 Trough [ng/mL]	376	3,433	321	4,465	**76.90**	72.30	81.78
gMean Trough of Weeks 4 to 48 [ng/mL]	448	3,354	438	4,107	**81.66**	78.16	85.33

In patients with intensive PK sampling, mean (± SD) steady state plasma concentrations of nevirapine after oral administration of nevirapine XR 400 mg QD (N=24) demonstrated extended release characteristics with less fluctuation (i. e., lower peak-trough ratio) than those observed in patients on nevirapine IR 200 mg BID (N=25) as shown in Figure below. The peak-to-trough fluctuation was 34.6% for nevirapine XR and 55.2% for nevirapine IR.

Figure 11:



Mean (SD) nevirapine plasma concentration-time profiles after oral administration of nevirapine XR 400 mg QD and nevirapine IR 200 mg BID on Day 28 in HIV-1 patient

The inter-patient variability was similar for the two formulations (see Tables below)

Table 26: Steady state PK sub study parameters of nevirapine XR 400 mg QD and nevirapine IR 200 mg BID on Day 28 under fasted conditions

PK Parameter		$t_{max,ss}$ [h]	$C_{max,ss}$ [ng/mL]	$C_{min,ss}$ [ng/mL]	$AUC_{0-24,ss}$ [ng·h/mL]	CL/F_{ss} [mL/min]
NVP XR 400 mg QD	Mean	6.51	3,940	2,760	79,200	94.6
N = 24	CV [%]	**104**	**29.1**	**34.3**	**29.5**	**40.6**
NVP IR 200 mg BID	Mean	2.08	5,660	3,350	103,000	72.8
N = 25	CV [%]	**43.4**	**26.5**	**33.8**	**29.9**	**49.7**

Table 27: Multiple dose PK parameters of nevirapine XR tablets 400 mg QD and IR tablets 200 mg BID in HIV-1 patients at Week 4 – PK sub-study results

Parameter		NVP XR 400 mg QD N = 24	NVP IR 200 mg BID N = 25	Ratio gMean XR/IR (%)
$AUC_{0-24,ss}$ [ng·h/mL]	Mean	79,200	103,000	
	CV [%]	29.5	29.9	
	gMean	75,300	98,200	76.7
$C_{min,ss}$ [ng/mL]	Mean	2,760	3,350	
	CV [%]	34.3	33.8	
	gMean	2,580	3,120	82.7
$C_{max,ss}$ [ng/mL]	Mean	3,940	5,660	
	CV [%]	29.1	26.5	
	gMean	3,770	5,460	69.0
Fluctuation (PTF) [%]	Mean	37.8	57.4	
	CV [%]	44.7	35.8	
	gMean	34.5	55.2	62.5
$t_{max,ss}$ [h]	Mean	6.51	2.08	
	CV [%]	104	43.4	
	gMean	4.25	1.89	225
CL/F_{ss} [mL/min]	Mean	94.6	72.8	
	CV [%]	40.6	49.7	
	gMean	88.5	67.9	130
C_{avg} [ng/mL]	Mean	3,330	4,300	
	CV [%]	29.5	29.9	
	gMean	3,140	4,090	76.8

Conclusions:

In 1100.1486, plasma concentrations of nevirapine XR 400 mg QD further demonstrated extended release characteristics of the nevirapine XR tablet formulation with less peak- to-trough fluctuation, and were generally lower than those of the nevirapine IR 200 mg BID.

Nevirapine XR to IR trough geometric mean ratio was 81.7% for the geometric mean of Weeks 4 to 48, and 76.9% for Week 48. The 10th percentile trough concentrations for nevirapine XR from Week 4 to Week 48 were all above 1,800 ng/mL, which is at least 13-fold higher than the IC90 for wild type HIV-1 virus. The nevirapine XR group showed non-inferior efficacy compared to the nevirapine IR group with a trend toward superiority, indicative of nevirapine XR delivering adequate nevirapine exposure. The relative trough exposure of nevirapine XR (compared to IR) was consistent among gender, race, region and baseline viral load stratum.

Study 1100.1518:

Title: An open-label, multiple dose, cross-over study to evaluate the steady-state pharmacokinetic parameters of nevirapine extended release tablets in HIV-1 infected children, with an optional extension phase

Objective:

To establish the pharmacokinetic parameters at steady-state of once-daily nevirapine prolonged release in children aged 3 to <18 years under fasting conditions

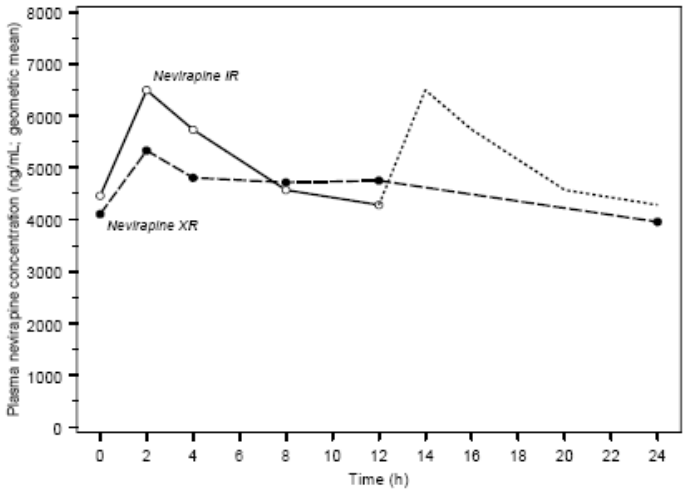
Methods:

This was an open label, multiple dose, non-randomised, cross-over study. HIV-1 infected patients treated for at least 18 weeks with nevirapine IR based regimen without protease inhibitors, and viral load <50 copies/mL. Patients were stratified into 3 age groups: ≥3 to <6 years, 6 to <12 years, and 12 to <18 years of age. Approximately 75 patients were to enter the study with 25 patients per each age group. All patients had trough plasma and saliva sampling to determine nevirapine concentrations. For the PK sub-study, at least the first 12 patients entered into the 3 to <6 years old age group and the first 10 patients entered into each of the two remaining age groups were assigned to perform post-dose plasma and saliva PK sampling to determine a full nevirapine profile at steady state. Following screening at baseline, qualified children and adolescents were stratified according to age and received nevirapine IR for at least 10 days (run-in phase) prior to the collection of a 12-hour nevirapine concentration-time profile on study Day 11 for PK analysis. On Day 12 nevirapine IR treatment was switched to nevirapine XR. All patients received nevirapine XR for 9 days prior to the collection of a 24-hour nevirapine concentration-time profile on study Days 21 and 22 for pharmacokinetic analysis. Plasma and saliva nevirapine concentrations were determined by a validated HPLC-MS/MS assay at with a lower limit of quantitation of 50 ng/mL. Full details of the assay can be found in the study report.

Results:

Geometric mean nevirapine plasma concentration-time profiles after oral administration of nevirapine XR QD and IR BID in paediatric patients aged 3 to <18 years are depicted in Figure below. The nevirapine XR QD profile appears to be more constant than the IR BID profile, suggesting nevirapine was slowly released and absorbed from XR tablets.

Figure 12:



Geometric mean nevirapine plasma concentration-time profiles after oral administration of nevirapine XR QD and IR BID in HIV-1 paediatric patients

In conclusion, the results of this study support the XR once daily dosing and demonstrate that the 100 mg nevirapine XR dose increment is appropriate and provides adequate dose adjustment for paediatric patients switching from twice daily nevirapine IR to once daily XR dosage forms. The target Cmin was achieved with the nevirapine XR formulation. Further, in children taking the XR formulation, the nevirapine exposure is similar to that observed in adult treatment-naive patients in the 48-week study (Study 1100.1486) as well as to that observed in patients switching from a nevirapine IR BID treatment in the 24-weeks study (Study 1100.1526). The efficacy results from these two studies demonstrate that this level of exposure is sufficient to ensure long term efficacy. Therefore, the data suggest that the XR formulation can also be used in paediatric populations.

Study 1100.1526:

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

Objective:

To assess the efficacy and safety of switching HIV-1 infected patients from a nevirapine IR based regimen to a nevirapine XR based regimen.

Method:

Open label, randomised, parallel group study. After successful screening, patients on a nevirapine IR-based HAART therapy were randomised with a 2:1 allocation ratio to either nevirapine XR 400 mg QD or nevirapine IR 200 mg BID. Patients remained on their previous background therapy.

Trough plasma samples were obtained at each visit and PK results until Week 24 (primary efficacy endpoint) are reported. Plasma nevirapine concentrations were determined by a validated HPLC-MS/MS assay with a lower limit of quantitation of 25 ng/mL Results were compared by treatment group, and summarized by gender, race, study region and background ARV therapy.

PK Results:

The mean trough concentrations were above 3,000 ng/ml and appeared to be relatively stable over the 24 week period for both nevirapine XR and nevirapine IR treatments (see Table below). The adjusted geometric mean of nevirapine XR was 3,493 ng/ml for trough concentrations of all weeks, and was 3,729 ng/mL for Week 24 (2nd table below). The nevirapine XR to IR ratio was 81.7% for the geometric mean of all troughs from all weeks was 82.9% for Week 24. The nevirapine XR trough concentrations were slightly lower than the nevirapine IR concentrations based on either the geometric mean of Weeks 2 to 24.

Table 28: Steady-state trough concentrations of nevirapine XR 400 mg QD compared to IR 200 mg BID in HIV-1 patients

Treatment		Trough NVP concentration (ng/mL) at Week					
		0	2	4	8	12	24
XR Tablet 400 mg QD	Mean	--[a]	3,740	3,580	4,060	3,980	4,040
	CV [%]	--	58.7	52.9	52.6	51.7	42.7
	gMean	--	3,270	3,220	3,680	3,590	3,730
	P10	--	1,840	1,840	2,260	2,080	2,290
	N	--	225	231	221	217	207
IR Tablet 200 mg BID	Mean	4210	3,980	4,040	4,360	4,470	4,340
	CV [%]	46.2	38.5	38.1	38.3	39.1	37.8
	gMean	3730	3,710	3,770	4,080	4,160	4,070
	P10*	2130	2,240	2,310	2,630	2,550	2,510
	N	145	110	110	113	110	110

Table 29: Nevirapine XR/IR geometric mean ratios (%) of trough plasma concentrations in HIV-1 patients

Parameter	Test: NVP XR 400 mg QD		Reference: NVP IR 200 mg BID		Adjusted gMean Ratio (Test/ Reference)	90% Confidence Interval	
	N	Adjusted gMean	N	Adjusted gMean	%	Lower limit (%)	Upper limit (%)
Week 24 Trough	207	3729.20	110	4066.97	**91.69**	85.01	98.91
gMean Trough of All Weeks	264	3492.58	149	3892.87	**89.72**	83.82	96.03

Conclusion:

In Study 1100.1526, nevirapine XR 400 mg QD trough concentrations were approximately 90% of nevirapine IR 200 mg BID. The nevirapine XR group showed non-inferiority to nevirapine IR group, indicative of nevirapine XR delivering adequate trough drug exposure. Pharmacokinetic as well as efficacy results support the switch from nevirapine IR twice-daily to nevirapine XR once-daily

Special populations

- Gender and Race

The plasma nevirapine trough concentrations from Phase III Study 1100.1486 were stratified by demographics at different weeks during the study. Compared to nevirapine IR, the XR drug product demonstrated consistent in vivo performance. Relative trough nevirapine concentrations in patients with different demographic backgrounds are summarized in Table below. The relative trough ratios of nevirapine XR to IR are mostly around 80% from Week 4 through Week 48 for Study 1100.1486. The XR/IR trough concentration ratios by demographics are found to be also consistent, albeit slightly higher (around 90%), for Study 1100.1526

Table 30: Nevirapine XR/IR geometric mean ratios (%) of trough plasma concentrations in HIV-1 patients with different demographic background and baseline viral load stratum in Study 1100.1486

	Week	4	6	8	12	16	24	32	40	48
Gender	Female	90.0	87.1	78.1	79.6	78.4	74.8	88.9	90.9	83.5
	Male	81.5	79.1	80.5	81.6	80.4	78.5	82.4	82.0	76.1
Race	Black	84.8	84.1	91.9	84.7	79.8	76.0	85.6	90.8	77.0
	White	82.0	79.6	76.8	79.3	80.1	79.1	82.9	81.7	77.4
Study region	Africa	78.3	84.6	82.3	91.1	77.2	71.9	87.5	93.5	68.3
	Europe	86.9	81.0	81.9	86.0	83.8	82.8	85.3	83.8	81.1
	Latin America	79.9	82.6	72.7	75.9	81.2	74.5	82.5	85.6	70.1
	N. America/Australia	--[a]	78.6	81.2	74.0	77.5	74.3	80.4	80.8	79.5
Baseline VL	≤ 100,000	82.5	80.9	83.2	79.3	80.3	78.1	82.0	85.1	78.9
	> 100,000	83.3	79.3	74.3	83.5	79.9	76.6	84.5	79.0	73.6

[a] Descriptive statistics were calculated only when at least 2/3 of the individuals have values within each group.

The demographic differences in nevirapine drug exposure are summarized in Table below, in which the geometric mean of trough concentrations between different demographic groups are compared (both for nevirapine XR and IR) by means of a ratio. Both nevirapine IR and XR show the same trend in demographic difference when two specific demographic groups are compared. Black patients tend to have higher nevirapine trough concentrations (approximately 30%) than white patients, whereas female patients appear to have higher concentrations (approximately 20-30%) than male patients in both XR and IR treatment groups. Also, Latin American patients appeared to have higher nevirapine trough concentrations than either European or North American-Australian patients in both XR and IR treatment groups. No apparent differences were observed between European and North American-Australian patients or patients with different baseline viral load stratum.

Table 31: Demographic ratios (%) of geometric mean plasma nevirapine trough concentrations for nevirapine XR 400 mg QD and nevirapine IR 200 mg BID – Study 1100.1486

		Average of Weeks 4 to 48
Africa / N.America-Australia	IR	147.0
	XR	153.3
Africa / EU	IR	143.5
	XR	139.5
Africa / Latin America	IR	119.4
	XR	124.1
Black / White	IR	129.2
	XR	135.4
Female / Male	IR	123.4
	XR	128.1
Latin America / EU	IR	120.2
	XR	112.4
Latin America / N.Amer-Australia	IR	122.8
	XR	122.5
EU / N.America-Australia	IR	102.4
	XR	108.9
Baseline VL ≤1000,000 / >100,000	IR	97.5
	XR	99.8

- Weight

No apparent relationship was found between nevirapine trough concentrations and age or body weight in both XR and IR treatment groups in adult patients from Studies 1100-1486 and 1526

- Elderly

No apparent relationship was found between nevirapine trough concentrations and age or body weight in both XR and IR treatment groups in adult patients from Studies 1100-1486 and 1526

- Children

In study 1100.1518 it is noted that children taking the XR formulation, the nevirapine exposure is similar to that observed in adult treatment-naïve patients in the 48-week study (Study 1100.1486) as well as to that observed in patients switching from a nevirapine IR BID treatment in the weeks study (study 1100.1526). The efficacy results from these studies show that this level of exposure is sufficient to ensure long term efficacy.

2.4.3. Pharmacodynamics

As this submission concerns an extension of marketing authorisation for a product with known mechanism of action and pharmacology for its active compound, no new pharmacodynamic data has been provided.

2.4.4. Discussion on clinical pharmacology

The applicant determined the extent and rate of absorption from different regions of the gastro-intestinal tract. Only the descending colon showed a low value for relative bioavailability as compared to an oral suspension, all the other (jejunum, ileum and ascending colon) showing a comparable degree of absorption (1.06 to 0.82).

By comparing the bioavailability with respect to the IR 200 mg form for 4 different XR formulations in 2 strengths (300 mg and 400 mg) yielding fast, medium and slow release rates, the applicant selected the KCR 20% and KCR 25% formulations for further development. The data obtained were used to

develop a level A in vitro/in vivo correlation (IVIVC), which was validated and used to establish dissolution specifications, on the basis of the prediction of AUC and Cmax. The validity of the in vivo drug release and in vitro drug release correlation (IVIVC) was confirmed.

Two other strengths for paediatric use (50 mg and 100 mg) were developed using the same formulation blend and shown to yield comparable bioavailability in 2 Phase I studies, but not strict bioequivalence, the 50 mg tablet being 6-11% greater in exposure than that of the 100 mg tablet. Results from PK sub-studies included in 3 Phase III clinical efficacy and safety studies suggest that these differences have no impact on the performance of these formulations.

No dose dumping was observed from the individual profiles and inter-individual variability was similar to the IR tablet.

Food effect was studied by establishing the steady state pharmacokinetic profiles and relative bioavailability of 2 different nevirapine XR formulations (KCR 20 and 25%), in two dose strengths (300 and 400 mg), under fasting and fed conditions, in comparison to nevirapine IR. The KCR 25%, 400 mg formulation was selected for clinical development sowing extended release characteristics. Exposure and rate of absorption were ca. 20% higher in fed state and Cmin,ss was ca. 10% higher. On the other hand this formulation in fed state is strictly bioequivalent to the IR formulation in fasted state. The applicant justified the use of a steady-state study because it is not ethical to give more than one dose to healthy volunteers (due to tolerability reasons) or to perform a cross-over study with a wash-out period in HIV infected patients (risk of generating resistance). Therefore, steady-state conditions are more relevant to test the food effect. Furthermore, during these steady-state studies, no clinical relevant food effect has been noted after administration of a high-fat meal. Thus it was concluded that the SmPC should not be amended.

Dose proportionality has been established for the 100 mg tablet but not for the 50 mg one. However, the applicant provided further reassurance regarding dose proportionality between the 100 mg and the 400 mg strength by providing sound reasons for excluding subject # 4. Furthermore, the 100 mg tablet intended for paediatric use is dose proportional to the 400 mg tablet and both the 100 mg and 50 mg strengths are made from the common formulation blend. It is stated that the in vivo drug release rates were consistent with the in vitro drug release dissolution profiles for the 50 mg and 100 mg strengths. Since the applicant states that: "From a pharmacokinetic perspective the nevirapine 50 and 100 mg XR tablets are clinically interchangeable and can be used once-daily in place of nevirapine IR twice daily tablets or suspension on a paediatric daily dose basis", still some doubts persist on the extrapolation of the investigated properties of the 400 mg strength, in particular the IVIVC and dissolution specifications, to the 100 mg and 50 mg strengths, because they are not strictly bioequivalent and dose proportionality was not investigated for the 50 mg strength. The applicant however argued that it has been demonstrated similar relative bioavailability between the 50mg and the 100mg XR tablets and claims interchangeability between the two tablets for paediatric use only. This is acceptable, as long as the IVIVC established for the 400mg tablet is not extended to the 50mg and 100mg tablets. Waiving the requirement for future BE-studies in case of major formulation changes for the 400 mg strength on the basis of the established IVIVC is not granted.

A summary of available data for overall and intra-subject variability is compiled in the table below. These values are similar or somewhat lower than the values observed for nevirapine 200 mg IR.

Table 32:

Variability (CV%)	Adult (400 mg)			Paediatric (100 mg)		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Intra-subject	17.9	17.4	22.0	26.8	36.2	29.5
Overall (1489)	45.1	42.3	47.6	--	--	--
Overall (1486)	29.5	29.1	24.3	--	--	--

Nevirapine terminal elimination half-life in plasma following a single dose administration was approximately 40 to 45 h. The half-life did not differ between nevirapine XR and nevirapine IR formulations.

The combination of nevirapine relatively long steady state half life and the BID dosing of the IR tablet results in a small peak-to-trough ratio of 1.9. Development of the nevirapine prolonged release once-daily formulation results in a further reduction of the peak-to-trough ratio to 1.5, attaining more stable plasma concentrations despite the larger dosing interval (24 h instead of 12 h).

Nevirapine is an enzyme inducer and can induce its own CYP3A and CYP2B6 mediated metabolism, which leads to an approximately 1.5- to 2-fold increase in the apparent oral clearance (CL/F) of nevirapine as treatment continues from the first dose to steady state. Auto-induction also results in a corresponding decrease in the terminal half life of nevirapine in plasma to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

In spite of auto-induction of CYP3A and 2B6, the reduction in half-life (from 40-45 h to 25-30 h), there is no impact on the slow release characteristics of nevirapine XR and the accumulation is therefore independent of formulation.

Three Phase III studies included PK intensive sub-studies in adult (1100.1486 and 1526) and paediatric populations (1100.1518).

Nevirapine prolonged release tablets show release characteristics with a lower (81.7%) trough concentration as compared to the IR formulation, still well above IC90 for wild type HIV 1 virus in study 1100-1486. From studies 1100.1518 and 1100.1526, both the paediatric 100 mg XR and the adult 400 mg XR formulations showed similar performance when compared to the IR formulation. The following issues have been further addressed by the applicant during the procedure (detailed discussion not provided in this assessment report):

(1) In order to support the statement that trough concentration is still well above IC90 for wild type HIV 1 virus, the MAH clarified how the threshold for Ctrough of the XR formulation was established.

It is stated that it is 13-fold higher than IC90 for wild-type HIV. The MAH clarified that this holds true also for (laboratory) virus strains with any resistance mutations by arguing that all the major nevirapine resistance mutations, such as Y181C or K103N, result in large shifts in susceptibility, and so marginal differences in trough concentrations will not result in meaningfully different barriers to resistance and that, since the once daily dosing is more convenient, adherence may be improved, and with improvement in adherence we would expect less emergence of resistance and improvement in antiviral efficacy of the XR formulation.

(2) the percentage of patients not achieving the PK target has been provided by the MAH, reassuring that this percentage was below clinical significance; and

(3) the applicant discussed the fact that no trough effect was found on the proportion of virologic responders by arguing that, as nevirapine binds directly to reverse transcriptase and blocks the RNA-dependant and DNA-dependant polymerase activities, as nNRTIs are active without transformation and their plasma concentration reflects the intracellular concentration of the drug, nevirapine plasma trough concentrations from 1.0 µg/ml (10 fold>IC90 of nevirapine for wild type virus) and above are comparable to nevirapine intracellular concentrations and therefore explain why no trough effect can be found for virologic responders.

Only race, gender, age and body weight have been analysed for nevirapine XR in comparison with data from the IR formulation. The findings point to the conclusion that both nevirapine IR and XR show the same trend in demographic difference when two specific demographic groups are compared.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics of the final nevirapine XR formulation administered as 400 mg QD in HIV-1 patients demonstrated consistent prolonged release characteristics with less fluctuation in the 24 hour PK profile than observed with the nevirapine IR 200 mg product. Nevirapine XR delivers nevirapine slowly in a controlled manner, resulting in extending the absorption to the entire intestinal tract (including the colon) without affecting the pharmacokinetic variability. No dose dumping was observed for nevirapine XR, neither following single dose nor during multiple administrations.

Food co-administration with nevirapine prolonged release tablets resulted in a slight increase of bioavailability by approximately 20% for AUC0-24,ss and Cmax,ss without any evidence of dose dumping or increase in variability. The extent of the increase due to a high fat meal was considered not clinically relevant and the nevirapine XR drug product can be taken without any food restrictions. Drug metabolism of nevirapine was found to be unchanged independent of the type of formulation administered.

Nevirapine XR drug product has slightly lower relative bioavailability (around 80% of AUC) compared to the nevirapine IR tablet. However, nevirapine prolonged release tablets perform consistently well during multiple dosing in HIV-1 patients along with background antiretroviral therapy with adequate drug exposure, meeting the target steady state exposure (trough concentration and Cmin,ss) expected to provide good viral suppression.

The relative bioavailability of nevirapine XR drug product was also consistent among HIV-1 patients with different demographics or background ARV therapy. Overall, the once-a-day nevirapine XR drug product resulted in adequate and more uniform plasma concentrations compared to the twice-a-day nevirapine IR product, and is expected to improve convenience and facilitate treatment adherence.

In paediatric HIV-1 patients aged 3 to <18 years the nevirapine prolonged release drug products performed equally well, achieving similar or slightly higher exposure levels in children as previously established in adult patients. Pharmacokinetic results support the once daily dosing of nevirapine XR in paediatric patients.

The steady state trough concentration (Cpre,ss) of the drug in plasma is considered the most important pharmacokinetic parameter for achieving and maintaining HIV-1 virus suppression with an NNRTI based regimen. Previous studies with nevirapine showed that maintenance of Cpre,ss above a lowest limit of 1,000 ng/mL should result in no loss of efficacy. The main phase III trial, which evaluated safety, efficacy and PK of nevirapine IR versus nevirapine XR in HIV-1 infected adult patients (Study 1100.1486) showed that nevirapine XR trough (Cpre,ss) concentrations over the 48 week period were stable (gMean across the weeks was 3,354 ng/mL). In the paediatric study, study 1100.1518, the overall steady state nevirapine gMean Cpre,ss was 4,160 ng/mL (n=78). The gMean

Cpre,ss for XR analyzed either by age group or dose group was well above the target concentration of above 3,000 ng/ml.

Level A IVIVIC has been established on the basis of a parallel study. This has been justified and the internal and external validation provided prediction errors of < 10%. This can be used to establish dissolution testing specifications.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

The clinical efficacy for the nevirapine prolonged release (XR) programme is established based on two Phase III controlled studies conducted in adult patients with human immunodeficiency virus, Type 1 (HIV-1) infection: Studies 1100.1486 "VERxVE" [U10-3212-01] and 1100.1526 "TRANxITION" [U10-3028-01]. The formulation and dose for these Phase III studies were based on a multiple-dose Phase Ib study, Study 1100.1489 [U08-2197-01], which evaluated 2 formulations in 2 dose strengths. Additionally, a Phase I clinical trial was conducted in HIV-1 infected children ages 3 to <18 years who were already on a nevirapine based antiretroviral regimen, in which the pharmacokinetic parameters of nevirapine XR were evaluated and short term efficacy was observed; Study 1100.1518 [U10-3350-01].

<u>Study 1100.1486:</u> A randomised, 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 mgBID neVirapinE immediate release in combination with Truvada in antiretroviral therapy naïve HIV-1 infected patients (VER*X*VE)

Study 1100.1486 is a randomised, double blind non-inferiority study assessing the efficacy and safety of nevirapine XR tablets administered once daily (QD) versus nevirapine immediate release (IR) tablets administered twice daily (BID), on a fixed background antiretroviral (ARV) regimen of tenofovir (TDF) and emtricitabine (FTC) (Truvada®) in treatment-naïve, HIV-1 infected patients [U10-3212-01]. The objective of the study is to evaluate the efficacy of nevirapine XR tablets, 400 mg QD, versus nevirapine IR tablets, 200 mg BID, in ARV-naïve HIV-1 infected patients after 48 weeks of treatment. The study duration is 48 weeks, with extended treatment up to 144 weeks. 1068 patients entered the lead-in phase of the study, and 1013 patients were randomized to one of the two treatments in a 1:1 ratio. Of these 1013 patients, 1011 were treated with blinded study drugs.

Methods

Outcomes/endpoints

The primary endpoint for Study 1100.1486 is a sustained virologic response at Week 48, using the LLOQ of 50 copies/ml HIV-1 RNA for viral load.

A virologic response is defined as two consecutive measurements of viral load <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 is defined as 48 ± 4 weeks from the day a patient started the lead-in treatment (nevirapine IR QD for 2 weeks).

A virologic rebound is defined as two consecutive measurements of a viral load of ≥50 copies/ml, at least 2 weeks apart, following a virologic response.

Patients, who died, were lost to follow-up, or changed ARV drugs due to toxicity/intolerance that was not attributable to the allowed background ARV therapies, were considered treatment failures at the time of those events.

Supplemental SNAPSHOT analyses

Patients with a viral load < LLOQ in the week window [48 – 4, 48 + 6] were classified as virologic responders.

Virologic outcome at the specified week window was classified into 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 window but on study.

Antiretroviral background therapy substitutions, permitted per protocol for documented toxicity reasons, were permitted on or before the first trial visit without penalty. If the ARV background therapy substitutions for toxicity reasons occurred after the first trial visit, then patients were considered virologic failures if they had a HIV-1 viral load >50 copies/ml at the time of the switch.

Key secondary endpoint was: time to loss of virologic response (LLOQ=50 copies/ml) - The time to loss of virologic response is defined as the time between the start of treatment and the confirmed virologic rebound.

Other secondary endpoints

Sustained virologic response at Week 48 (LLOQ=400 copies/ml)

The definition for this endpoint is the same as the primary endpoint, except that the LLOQ of 400 copies/ml is used.

Time to loss of virologic response (LLOQ=400 copies/ml)

The definition for this endpoint is the same as the key secondary endpoint, except that the LLOQ of 400 copies/ml is used.

Sustained virologic response at each visit (LLOQ=50 copies/ml)

The proportion of patients with a sustained virologic response at each visit for each treatment group was calculated using the definitions of a non-responder noted below.

Definitions of a Non-responder

For each visit, a subject with the following events prior to or at this visit will be considered as a non-responder or failure for that visit if any of the following events occur:

a) Death

b) Permanent discontinuation of the study drug or lost to follow-up

c) Introducing a new drug to the regimen

d) Have not achieved < LLOQ that was confirmed later for achieved confirmed < LLOQ status but rebounded (i.e., two consecutive ≥ LLOQ copies/mL [the latter one possibly after the visit of interest], or one ≥ LLOQ copies/mL for the last available visit)

Time to confirmed virologic response

This is defined as the time between the start of lead-in treatment and the first viral load < LLOQ of a confirmed virologic response (two consecutive measurements of viral load < LLOQ, at least 2 weeks apart) prior to the time when the last patient is on treatment for 48 weeks. Patients without confirmed virologic response were considered censored at their last on-treatment visit.

Time to new AIDS or AIDS-related progression event or death (TAIDS)

Time to new AIDS or AIDS-related progression event or death is defined as the time from the start of treatment to the time when the new AIDS or AIDS-related progression event or death occurred, whichever came first. Patients with none of these events were considered censored at their last available follow-up visit.

Change from baseline in CD4+ cell count

The CD4+ cell counts were analyzed as absolute counts. The baseline for a CD4+ cell count was calculated based on the arithmetic mean of the last two measurements (if available) before the start of treatment with study drug; this value was used to calculate the change from baseline.

Treatment-emergent mutations

To characterize nevirapine resistance, patients failing virologically in Study 1100.1486 were selected for genotypic and phenotypic testing. For the purpose of classifying patients from whom on-treatment retention samples were selected for genotyping, virologic failure was defined as follows: viral load was never suppressed, viral load rebounded, or viral load was partially suppressed.

Viral samples successfully amplified were genotyped by Monogram Biosciences using their commercially available GeneSeq HIV assay. The GeneSeq algorithm for identifying resistance-associated amino acids and predicting resistance is based on published scientific literature and proprietary information from the Monogram Biosciences' phenotype-genotype database.

Of those patients genotyped, virus samples with amino acid substitutions other than those known to be associated with nevirapine resistance were phenotyped. All phenotypic testing was conducted by Monogram Biosciences using their commercially available Phenosense Assay. The phenotypic testing was performed to determine if previously unrecognized amino acid substitutions that confer reduced nevirapine susceptibility and could lead to virologic failure were observed with virologic failures in Study 1100.1486.

Blinding (masking)

Only study 1100.1486 is double blind.

Statistical methods

The primary efficacy analysis was the test of the non-inferiority of the nevirapine XR formulation to nevirapine IR with a non-inferiority margin Δ = -10%. A 95% confidence interval (CI) for the difference in the proportions of virologic response between nevirapine XR and nevirapine IR treatment groups was constructed using Cochran's statistic, stratified by baseline HIV-1 viral load, and with continuity correction for the variance. Non-inferiority of nevirapine XR to nevirapine IR treatment was established

if the lower bound of the CI was greater than -10%. Superiority was to be tested if non-inferiority was established. For the pharmacokinetic (PK) analysis, relative bioavailability was assessed, and the minimum and geometric mean (gMean) trough concentrations were calculated for all patients.

Results

Participant flow

A total of 1626 patients were enrolled into the 1100.1486 study. Of the 1068 patients who entered the study and were treated with the nevirapine IR 200 mg QD dose in the lead-in phase, 55 patients were not randomized. The majority of these 55 patients were not randomized due to AEs (38 patients).

The following table summarizes the disposition of patients after randomization through Week 48 in Study 1100.1486.

Table 33:

	NVP IR 200 BID	NVP XR 400 QD	Total
Randomized	508	505	1013
Treated with blinded dose [N (%)]	506 (100.0)	505 (100.0)	1011 (100.0)
Completed Week 48 visit [N (%)]	409 (80.8)	421 (83.4)	830 (82.1)
Prematurely discontinued prior to Week 48 visit [N (%)]	97 (19.2)	84 (16.6)	181 (17.9)
Reasons for discontinuation [N (%)]			
Death or events leading to death	3 (0.6)	1 (0.2)	4 (0.4)
Adverse events	42 (8.3)	32 (6.3)	74 (7.3)
Worsening of disease/condition under study	3 (0.6)	3 (0.6)	6 (0.6)
Worsening of other pre-existing disease/condition	1 (0.2)	2 (0.4)	3 (0.3)
Other adverse event	38 (7.5)	27 (5.3)	65 (6.4)
Lost to follow-up	7 (1.4)	8 (1.6)	15 (1.5)
Consent withdrawn	9 (1.8)	4 (0.8)	13 (1.3)
Noncompliance	9 (1.8)	6 (1.2)	15 (1.5)
Lack of efficacy[a]	26 (5.1)	24 (4.8)	50 (4.9)
Pregnancy[a]	0 (0.0)	6 (1.2)	6 (0.6)
Other	1 (0.2)	3 (0.6)	4 (0.4)

[a] According to the comment field of the "Other" category on the electronic Case Report Form (eCRF) termination of the trial medication page.

Source data: [U10-3212-01, Module 5.3.5.1, Table 15.1.1: 4]

Outcomes and estimation

Primary endpoint

Sustained virologic response at Week 48 (LLOQ = 50 copies/ml)

As showed in the table below the adjusted difference was 4.9% (95% CI -0.1%, 10.0%), favoring nevirapine XR treatment. The lower bound of -0.1% indicated a trend toward superiority of nevirapine XR to nevirapine IR treatment.

Table 34: Comparison of proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm), Study 1100.1486 - FAS

	No. with response/total No. (%)		Difference in % (95% CI)	P-value for non-inferiority test
	NVP IR 200 BID	NVP XR 400 QD		
Background HIV-1 viral load stratum (copies/mL)				
≤100, 000	240/303 (79.2)	267/311 (85.9)	6.6 (0.7, 12.6)	
>100, 000	144/203 (70.9)	142/194 (73.2)	2.3 (-6.6, 11.1)	
Total	384/506 (75.9)	409/505 (81.0)	4.9 (-0.1, 10.0)[a]	<0.0001[b]

[a] Based on Cochran's statistic with continuity correction for the variance calculation.

[b] The non-inferiority test was for the hypothesis $\pi_1 - \pi_0 \leq -0.10$, where π_1 is the proportion of sustained virologic responders in the nevirapine XR group and π_0 is the proportion of sustained virologic responders in the nevirapine IR group

Source data: [U10-3212-01, Module 5.3.5.1, Table 15.2.1: 4]

A summary of the overall outcomes at Week 48 is given in the next table.

Table 35: Summary of study outcomes at Week 48 with LLOQ=50 copies/mL (Amplicor-corrected, TLOVR algorithm), Study 1100.1486 - FAS

Outcome (LLOQ = 50 copies/mL)	NVP IR 200 BID N (%)	NVP XR 400 QD N (%)
Total	506 (100.0)	505 (100.0)
Virologic responder	384 (75.9)	409 (81.0)
Failure	122 (24.1)	96 (19.0)
Virologic failure[a]	30 (5.9)	16 (3.2)
Never suppressed through Week 48	13 (2.6)	5 (1.0)
Rebound	17 (3.4)	11 (2.2)
Discontinued study drug prior to Week 48	92 (18.2)	80 (15.8)
Death or events leading to death	3 (0.6)	1 (0.2)
Adverse events	42 (8.3)	32 (6.3)
Lost to follow-up	6 (1.2)	7 (1.4)
Consent withdrawn	9 (1.8)	3 (0.6)
Noncompliance	7 (1.4)	5 (1.0)
Lack of efficacy	24 (4.7)	23 (4.6)
Pregnancy	0 (--)	6 (1.2)
Other	1 (0.2)	3 (0.6)

[a]Virologic failure has a higher priority over discontinuation in the case of multiple events.
Source data: [U10-3212-01, Module 5.3.5.1, Table 15.2.1: 1]

Secondary analyses of the primary endpoint

Secondary analyses of the primary endpoint were performed using combinations of different assay profiles (TaqMan, Amplicor-corrected), different algorithms to define virologic responders (TLOVR algorithm, SNAPSHOT approach), and different analysis data sets (FAS, PPS,) to test the non-inferiority of nevirapine XR to nevirapine IR (Table 36).

Table 36: Results of secondary analyses of virologic response at Week 48 using LLOQ = 50 copies/mL, Study 1100.1486

Analysis Dataset	Method	Assay	No. with response/total No. (%) IR 200 BID	No. with response/total No. (%) XR 400 QD	Difference in % (95% CI)[a]
FAS	TLOVR	TaqMan-only	368/506 (72.7)	386/505 (76.4)	3.5 (-1.8, 8.8)
FAS	SNAPSHOT[b]	Amplicor-corrected	379/506 (74.9)	404/505 (80.0)	4.9 (-0.2, 10.1)
FAS	SNAPSHOT[b]	TaqMan-only	361/506 (71.3)	377/505 (74.7)	3.0 (-2.4, 8.4)
PPS	TLOVR	Amplicor-corrected	369/481 (76.7)	395/485 (81.4)	4.4 (-0.7, 9.5)

[a] Based on Cochran's statistic with continuity correction for the variance calculation.
[b] The pre-specified SNAPSHOT approach uses the 44-52 week window.
Source data: [U10-3212-01, Module 5.3.5.1, Tables 15.2.1: 5 – 8]

Supplemental SNAPSHOT analysis of the primary endpoint

Using the supplemental SNAPSHOT approach and the Amplicor-corrected profile, 75.1% (380/506) and 80.2% (405/505) of patients in the nevirapine IR and XR groups, respectively, were considered virologic responders at Week 48. This finding was consistent with the results from the primary analysis of the primary endpoint.

The virologic failure rates were 13.2% and 10.7% in the nevirapine IR and XR groups, respectively. There were 11.7% and 9.1% patients in the nevirapine IR and XR groups, respectively, who had no virologic data in the Week 48 window (44-54 weeks).

Key secondary endpoint

Time to loss of virologic response

For the baseline viral load ≤100,000 copies/mL stratum the proportion of patients without loss of virologic response using LLOQ = 50 copies/mL was greater for the nevirapine XR group than the nevirapine IR group for all time points through Week 72 using the Amplicor-corrected assay profile. For the baseline viral load >100,000 copies/mL stratum, the proportions were comparable in the two treatment groups. The same pattern was observed when using the TaqMan-only assay profile.

Other secondary endpoints

Sustained virologic response at Week 24 (LLOQ = 50 copies/ml)

The nevirapine XR group tended to have a higher proportion of patients with a sustained virologic response (LLOQ=50 copies/mL) at Week 24 compared with the nevirapine IR group.

Sustained virologic response at Week 48 (LLOQ = 400 copies/ml)

The nevirapine XR group tended to have a higher proportion of patients with a sustained virologic response (using LLOQ=400 copies/mL) compared with the nevirapine IR group, when analyzed using the TLOVR algorithm. This finding at Week 48 was independent of the algorithms used to define virologic response and HIV-1 RNA assays. The fact that the lower limits of the 95% CIs were greater than -2% confirmed the non-inferiority of nevirapine XR to nevirapine IR at Week 48.

Sustained virologic response by visit

In the analysis of virologic responders (LLOQ = 50 copies/mL) at each visit using the TLOVR algorithm and the Amplicor-corrected assay, the proportion of virologic responders increased steeply from Week 0 to Week 24 for both the nevirapine IR and XR groups. Starting from Week 24, the proportion of responders in the nevirapine XR group kept increasing and peaked at Week 48. A similar pattern was observed for the TaqMan only assay. When LLOQ = 400 copies/ml was used for the definition of virologic response, the response proportion peaked at Week 16 for both groups (84.6% for nevirapine IR and 88.3% for nevirapine XR) then gradually decreased to 78.9% for the IR group and 83.2% for the XR group. Overall, the nevirapine XR group tended to have a higher response proportion than the IR group from Week 2 to Week 48.

Time to confirmed virologic response

Based on the Kaplan-Meier curves, the time it took for a patient to become a virologic responder (LLOQ = 50 copies/mL, Amplicor-corrected profile) was comparable for the nevirapine IR and XR groups for each baseline HIV-1 viral load stratum. The finding was consistent when using the TaqMan-only assay. Adjusted for baseline HIV-1 viral load stratum, there was no meaningful difference for time to confirmed virologic response between the two treatment groups for the Amplicor-corrected assay profile (LLOQ = 50 copies/mL). The finding was consistent when using the TaqMan-only assay profile (LLOQ = 50 copies/mL).

Change from baseline in CD4+ cell count at each visit

For mean changes in CD4+ cell count from baseline using LOCF values, a steep increase in CD4+ cell count from baseline was observed in the first 8 weeks for both treatment groups (+107 cells/mm3 for nevirapine IR and +111 cells/mm3 for nevirapine XR. At Week 48, the mean increase was +181 cells/mm3 for nevirapine IR and +192 cells/mm3 for nevirapine XR. Using the least square mean, the mean increase in CD4+ cell count at Week 48 was +184 cells/mm3 for the nevirapine IR group and +197 cells/mm3 for the nevirapine XR group. In general, when adjusted for baseline HIV-1 viral load stratum, the difference in the increase in CD4+ cell count for the two treatment groups was similar at Week 48 for the nevirapine XR group compared with the nevirapine IR group, regardless of whether using observed or LOCF values.

Time to new AIDS or AIDS-related progression event or death

There were 19 (3.8%) patients with new AIDS events in the nevirapine IR group versus 12 (2.4%) in the nevirapine XR group; there were 2 AIDS-related deaths in the nevirapine IR group versus none in the nevirapine XR group. Based on the Kaplan-Meier curves, the cumulative probability of having a new AIDS or AIDS-related progression event or death was comparable between the nevirapine IR and XR groups during the first 6 weeks of treatment. The probability tended to be higher in the nevirapine IR group than the nevirapine XR group starting from Week 6 to the pre-specified Week 72. The hazard of having a new AIDS or AIDS-related progression event or death in the nevirapine XR group was 57% that of the nevirapine IR group, with a 95% CI of 28%, 116%, indicating the difference observed was not conclusive.

Ancillary analyses

Subgroup analyses

The primary endpoint was investigated in the following subgroups:

- Baseline demographic characteristics of age, gender, race, ethnicity, and region;
- Baseline characteristics of HIV-1 viral load stratum, CD4+ cell count, HIV-1 subtype, and CDC class;
- Lead-in duration.

Main results are summarized on the following tables.

Table 37: Proportion of virologic response at Week 48 using LLOQ=50 copies/mL by baseline demographics (Amplicor-corrected TLOVR algorithm), Study 1100.1486 - FAS

	No. with response/total No. (%)	
	NVP IR 200 BID	NVP XR 400 QD
Total number of patients	384/506 (75.9)	409/505 (81.0)
Age (years)		
18-40	235/314 (74.8)	242/300 (80.7)
41-55	129/165 (78.2)	149/181 (82.3)
>55	20/27 (74.1)	18/24 (75.0)
Gender		
Male	329/431 (76.3)	353/431 (81.9)
Female	55/75 (73.3)	56/74 (75.7)
Race		
White	285/374 (76.2)	321/387 (82.9)
Black	84/113 (74.3)	72/ 94 (76.6)
Asian	10/ 13 (76.9)	11/ 15 (73.3)
Other	5/6 (83.3)	5/9 (55.6)
Hispanic/Latino		
Yes	82/108 (75.9)	96/115 (83.5)
No	302/398 (75.9)	313/390 (80.3)
Region		
North America/Australia	114/148 (77.0)	114/141 (80.9)
Europe	185/252 (73.4)	204/257 (79.4)
Latin America	39/ 49 (79.6)	51/ 58 (87.9)
Africa	46/ 57 (80.7)	40/ 49 (81.6)

Source data: [U10-3212-01, Module 5.3.5.1, Table 15.2.1: 19]

Table 38: Study 1100.1486: Proportion of virologic response at Week 48 using LLOQ=50 copies/mL by baseline characteristics (Amplicor-corrected, TLOVR algorithm)

Baseline characteristics	No. with response/total No. (%)	
	NVP IR 200 BID	NVP XR 400 QD
Total number of patients	384/506 (75.9)	409/505 (81.0)
Baseline HIV-1 RNA stratum copies/mL [N (%)]		
≤100,000	240/303 (79.2)	267/311 (85.9)
>100,000	144/203 (70.9)	142/194 (73.2)
Baseline CD4+ count (cells/mm^3) [N (%)]		
≤50	0/1 (0)	0/0 (--)
>50 - 200	144/199 (72.4)	137/179 (76.5)
>200 - 350	208/263 (79.1)	236/282 (83.7)
>350 - 399[a]	24/31 (77.4)	27/34 (79.4)
≥400[a]	7/11 (63.6)	7/8 (87.5)
Missing	1/1 (100.0)	2/2 (100.0)

Virologic response and trough plasma concentrations

The effect of trough concentrations on the sustained virologic response at Week 48 was evaluated using gMean trough level, which was defined as the geometric mean of all available steady-state troughs from Week 4 to Week 48 for each patient.

Overall, there were no race, gender or region interactions with trough levels when the minimum steady-state trough was used.

Virological resistance

During Study 1100.1486, 86 patients had on-treatment retention samples selected for genotyping based on a review of their virologic profiles. These included 54 patients in the nevirapine IR treatment group and 32 patients in the nevirapine XR group. The majority of these patients had discontinued study drug treatment due to lack of efficacy (24 and 16 patients in the nevirapine IR and XR group, respectively) and AEs (15 and 6 patients in the nevirapine IR and XR group, respectively), and for other reasons, such as noncompliance, loss to follow-up or consent withdrawal (5 and 7 patients in the nevirapine IR and XR group, respectively). Three (3) patients (all in the nevirapine IR group) had viral loads that which were never suppressed through Week 48, and 6 patients (4 in the nevirapine IR and 2 in the nevirapine XR group) were rebounders, having achieved a viral load nadir of HIV-1 RNA of <400 copies/mL, with a subsequent viral load increase to >1000 copies/mL. In addition, 4 patients (3 in the nevirapine IR and 1 in the nevirapine XR group) were actually responders, but experienced a transient increase in viral load during the course of the study, and thus, had on-treatment genotyping.

The pattern of resistance developed to the drugs used in the treatment regimen was the same in both the nevirapine IR and nevirapine XR group. Overall, 41.9% (36/86) of the resistance testing patients did not have resistant virus at failure. All of the remaining resistance testing patients (50/86, 58.1%) showed resistance to nevirapine, with the majority showing resistance to FTC (43 patients, 50% of all

resistance testing patients). Tenofovir (TDF) resistance was observed in 13 of the 43 resistance testing patients whose virus was resistant to nevirapine and FTC, 15.1% of all resistance testing patients).

In further evaluation of cross resistance among the more widely used NNRTIs (nevirapine, efavirenz [EFV], and etravirine [ETR]) at failure, no difference in resistance related to the study treatment, nevirapine IR or XR was observed. Etravirine resistance was observed in 5 patients who had not developed nevirapine resistance. Of the 50 patients with nevirapine-resistant virus at failure, 22.0% (11/50) were also resistant to EFV but not ETR, 44.0% (22/50) were also resistant to ETR but not EFV, and the remaining 34% (17/50) were resistant to all 3 NNRTIs.

Two new substitutions on nevirapine resistance codons were identified: Y181I and Y188N. Patients with these substitutions had substantial decreases in nevirapine susceptibility associated with the emergence of these substitutions.

Study 1100.1526: 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

Study 1100.1526 is an open-label, randomised, parallel-group study [U10-3028-01]. The objective of this study is to assess the efficacy and safety of switching treatment-experienced HIV-1infected patients from a Viramune (nevirapine IR) administered 200 mg BID regimen to nevirapine XR 400 mg tablets administered QD. Treatment-experienced patients, who were already on a nevirapine IR BID regimen and were virologically suppressed for at least 18 weeks at the time of enrollment and had a viral load of <50 copies/mL, were randomized to either nevirapine XR 400 mg QD or nevirapine IR 200 mg BID. The duration of the study is 48 weeks, with extended treatment up to 144 weeks. A total of 445 patients entered the study and were randomised in a 2:1 ratio (nevirapine XR : nevirapine IR), and 443 were treated with study drugs.

Methods

Outcomes/endpoints

The **primary endpoint** for Study 1100.1526 is a sustained virologic response through Week 24, using the LLOQ=50 copies/ml for viral load.

A virologic response is defined as two consecutive measurements of viral load <50 copies/ml, at least 2 weeks apart. A sustained virologic response had no virologic rebound or change of ARV therapy (defined below) through Week 24. For Study 1100.1526, the time window of Week 24 is defined as 24 ± 4 weeks from the day a patient started study treatment.

A virologic rebound is defined as two consecutive measurements of a viral load of ≥50 copies/ml, at least 2 weeks apart, following a virologic response.

Patients, who died, were lost to follow-up, or changed ARV drugs due to toxicity/intolerance that was not attributable to the allowed background ARV therapies, were considered treatment failures at the time of those events.

Supplemental SNAPSHOT analyses

> Patients with a viral load < LLOQ in the 24 ± 6 week window were classified as virologic responders.
>
> Virologic outcome at the specified week window was classified into 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 window but on study.

Antiretroviral background therapy substitutions, permitted per protocol for documented toxicity reasons, were permitted on or before the first trial visit without penalty. If the ARV background therapy substitutions for toxicity reasons occurred after the first trial visit, then patients were considered virologic failures if they had a HIV-1 viral load >50 copies/ml at the time of the switch.

Key secondary endpoint was: time to loss of virologic response (LLOQ=50 copies/ ml) - The time to loss of virologic response is defined as the time between the start of treatment and the confirmed virologic rebound.

Other secondary endpoints

Sustained virologic response at each visit (LLOQ=50 copies/ml)

The proportion of patients with a sustained virologic response at each visit for each treatment group was calculated using the definitions of a non-responder noted below.

Definitions of a Non-responder

For each visit, a subject with the following events prior to or at this visit will be considered as a non-responder or failure for that visit if any of the following events occur:

a) Death

b) Permanent discontinuation of the study drug or lost to follow-up

c) Introducing a new drug to the regimen

d) Have not achieved < LLOQ that was confirmed later for achieved confirmed < LLOQ status but rebounded (i.e., two consecutive ≥ LLOQ copies/mL [the latter one possibly after the visit of interest], or one ≥ LLOQ copies/mL for the last available visit)

Change from baseline in CD4+ cell count

The CD4+ cell counts were analyzed as absolute counts. The baseline for a CD4+ cell count was calculated based on the arithmetic mean of the last two measurements (if available) before the start of treatment with study drug; this value was used to calculate the change from baseline.

Blinding (masking)

Open label trial design

Statistical methods

The primary efficacy analysis was the test of the non-inferiority of the nevirapine XR formulation to nevirapine IR with a non-inferiority margin Δ = -12%. A 95% CI for the difference in the proportions of

virologic response between nevirapine XR and nevirapine IR treatment groups was constructed using Cochran's statistic, stratified by background therapy, and with continuity correction for the variance. Non-inferiority of nevirapine XR to nevirapine IR was established if the lower bound of the CI was greater than -12%. The -10% non-inferiority margin was added to the Trial Statistical Analysis Plan prior to the 24-week database lock and was used for secondary analyses. For the PK analysis, relative bioavailability was assessed and minimum and gMean steady state trough concentrations were determined.

Results

Participant flow

Of the 443 subjects who received at least one dose of study drug, 432 (97.5%) completed 24 weeks of study treatment. The proportion of patients completing 24 weeks of treatment was similar for the two groups: nevirapine IR group (97.3%) and nevirapine XR group (97.6%).

The following table summarizes the disposition of patients after randomization through Week 24 in Study 1100.1526.

Table 39:

	NVP IR 200 BID	NVP XR 400 QD	Total
Enrolled	NA	NA	499
Randomized	149	296	445
Treated [N (%)]	148 (100.0)	295 (100.0)	443 (100.0)
Completed Week 24 visit[a] [N (%)]	144 (97.3)	288 (97.6)	432 (97.5)
Prematurely discontinued prior to Week 24 visit [N (%)]	4 (2.7)	7 (2.4)	11 (2.5)
Reasons for discontinuation [N (%)]			
Death or events leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events			
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease/condition	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	3 (1.0)	3 (0.7)
Lost to follow-up	1 (0.7)	1 (0.3)	2 (0.5)
Consent withdrawn	1 (0.7)	0 (0.0)	1 (0.2)
Noncompliance	0 (0.0)	2 (0.7)	2 (0.5)
Lack of efficacy[b]	1 (0.7)	0 (0.0)	1 (0.2)
Pregnancy[b]	0 (0.0)	1 (0.3)	1 (0.2)
Other	1 (0.7)	0 (0.0)	1 (0.2)

[a] Including patients #1367 and #4653 who completed the Week 24 visit, but made the visit outside of the 24 +/- 4 weeks window.

[b] According to the comment field of the "Other" category on the eCRF termination of the trial medication page.

Source data: [U10-3028-01, Module 5.3.5.1, Table 15.1.1: 3]

Outcomes and estimation

Primary endpoint

Sustained virologic response at Week 48 (LLOQ = 50 copies/ml)

The adjusted difference was 1.0% (95% CI -4.3%, 6.2%). The -4.3% lower bound of the 95% CI demonstrated the non-inferiority of nevirapine XR to nevirapine IR treatment (pre-specified non-inferiority margin -12%) (Please refer to the next table).

Table 40: Comparison of virologic response at Week 24 using LLOQ=50 copies/mL (Amplicor-corrected, TLOVR algorithm), Study 1100.1526 - FAS

	No. of patients with response/total no. of patients (%)		Difference in % response (95% CI)
	NVP IR 200 BID	NVP XR 400 QD	
Background ARV			
Truvada®	77/82 (93.9)	145/158 (91.8)	-2.1 (-8.9, 4.6)
Combivir®	29/30 (96.7)	59/63 (93.7)	-3.0 (-11.8, 5.8)
Kivexa® / Epzicom™	31/36 (86.1)	72/74 (97.3)	11.2 (-0.7, 23.1)
Total	137/148 (92.6)	276/295 (93.6)	1.0 (-4.3, 6.2)[a]

[a] Based on Cochran's statistic with continuity correction for the variance calculation.
Source data: [U10-3028-01, Module 5.3.5.1, Table 15.2.1: 3]

Overall through Week 24, 92.6% of the patients in the nevirapine IR and 93.6% of the patients in the nevirapine XR group were responders (Table 41).

Table 41: Summary of study outcomes at Week 24 (LLOQ=50 copies/mL, Amplicor-corrected, TLOVR algorithm), Study 1100.1526 - FAS

Outcome (LLOQ = 50 copies/mL)	NVP IR 200 BID N (%)	NVP XR 400 QD N (%)
Total	148 (100.0)	295 (100.0)
Virologic responder	137 (92.6)	276 (93.6)
Failure	11 (7.4)	19 (6.4)
Virologic failure[a]	8 (5.4)	12 (4.1)
Rebound	5 (3.4)	10 (3.4)
Other[b]	3 (2.0)	2 (0.7)
Discontinued study drug prior to Week 24	3 (2.0)	7 (2.4)
Death or events that led to death	0 (--)	0 (--)
Adverse events	0 (--)	3 (1.0)
Loss to follow-up	1 (0.7)	1 (0.3)
Consent withdrawn	1 (0.7)	0 (--)
Noncompliance	0 (--)	2 (0.7)
Lack of efficacy	0 (--)	0 (--)
Pregnancy	0 (--)	1 (0.3)
Other	1 (0.7)	0 (--)

[a]Virologic failure has a higher priority over discontinuation in the case of multiple events.
[b]The Week 24 visit was out of the 24 ± 4 week window for patients #1367 and #4653 (both in the nevirapine XR group). The Week 24 visit viral load was missing for patients #1157 and #2545 (both in the nevirapine IR group). Patient #2144 (nevirapine IR group) missed the Week 24 visit, but continued thereafter.
Source data: [U10-3028-01, Module 5.3.5.1, Table 15.2.1:1, Listing 16.2.6.1]

Secondary analyses of the primary endpoint

Secondary analyses for the primary endpoint were performed using combinations of different analysis datasets, assays and methods (Table 42).

Table 42: Results of secondary analyses of virologic response at Week 24 using LLOQ=50 copies/mL, Study 1100.1526

Analysis Dataset	Method	Assay	No. with response/total No. (%) NVP IR 200 BID	NVP XR 400 QD	Difference in % (95% CI)[a]
FAS	TLOVR	TaqMan-only	133/148 (89.9)	269/295 (91.2)	1.3 (-4.7, 7.3)
FAS	SNAPSHOT[b]	Amplicor-corrected	139/148 (93.9)	281/295 (95.3)	1.3 (-3.5, 6.1)
FAS	SNAPSHOT[b]	TaqMan-only	137/148 (92.6)	279/295 (94.6)	2.0 (-3.2, 7.1)
PPS	TLOVR	Amplicor-corrected	136/147 (92.5)	274/293 (93.5)	1.0 (-4.3, 6.3)

[a] Based on Cochran's statistic with continuity correction for the variance calculation.
[b] The pre-specified SNAPSHOT approach uses the 20-28 week window.
Source data: [U10-3028-01, Module 5.3.5.1, Tables 15.2.1: 4-7]

Supplemental SNAPSHOT analysis of the primary endpoint

Using the supplemental SNAPSHOT approach with the 18-30 week window and the Amplicor-corrected profile, 93.9% (139/148) and 95.9% (283/295) patients in the nevirapine IR and XR groups, respectively, were virologic responders at Week 24. Compared with the pre-specified SNAPSHOT approach with the 20-28 week window for the primary endpoint, this broader window captured the same number of virologic responders for the nevirapine IR group but two additional virologic responders for the nevirapine XR group. The virologic failure rates were 2.0% and 1.7% for the nevirapine IR and XR groups, respectively. There were 4.1% and 2.4% patients in the nevirapine IR and XR groups, respectively, who had no virologic data in the Week 24 window (18-30 weeks).

Key secondary endpoint

Time to loss of virologic response

Based on the Kaplan-Meier curves, the proportion of patients without loss of virologic response (LLOQ=50 copies/mL, Amplicor-corrected assay profile) was similar for both treatment groups through Week 24. No significant difference in time to loss of virologic response was detected between the two treatment groups based on the Cox model, adjusting for background ARV therapy. For the Amplicor-corrected profile, the hazard ratio of nevirapine XR compared with nevirapine IR was 0.88 (95% CI 0.42, 1.86). The TaqMan-only analysis supported these findings with a hazard ratio of 0.89 (95% CI 0.47, 1.68).

Other secondary endpoints

Sustained virologic response by visit

The proportion of sustained virologic responders decreased slightly and gradually from Week 0 to Week 24. The two treatments showed very little difference.

Change from baseline in CD4+ cell count at each visit

At Week 24, the mean increase from baseline in CD4+ count was +50 cells/mm3 for nevirapine IR and +45 cells/mm3 for nevirapine XR, when LOCF values were used. The findings were similar when observed values were used for analysis. In general, when adjusted for background ARV therapy stratum, the difference in the increase in CD4+ cell count from baseline for the two treatment groups was similar at Week 24 for the nevirapine XR group compared with the nevirapine IR group, regardless of whether using observed or LOCF values.

Ancillary analyses

Subgroup analyses

The primary endpoint was investigated in the following subgroups:

- Baseline demographic characteristics, including age, gender, race, ethnicity, and region;
- Baseline characteristics, including baseline background therapy, CD4+ cell count, and HIV-1 baseline viral load, and CDC class, nevirapine as first Highly Active Antiretroviral Therapy (HAART) regimen, duration of previous nevirapine IR treatment, and type of previous background therapy prior to study medication.

Main results are summarized in the following tables.

Table 43: Proportion of patients with virologic response at Week 24 using LLOQ=50 copies/mL by baseline demographics (Amplicor-corrected, TLOVR algorithm) in Study 1100.1526 – FAS

	Number with response/total number (%)	
Baseline demographic characteristic	**NVP IR 200 BID**	**NVP XR 400 QD**
Total number of patients	137/148 (92.6)	276/295 (93.6)
Age (years)		
18-40	30/36 (83.3)	64/70 (91.4)
41-55	75/79 (94.9)	160/168 (95.2)
>55	32/ 33(97.0)	52/57 (91.2)
Gender		
Male	119/128 (93.0)	229/244 (93.9)
Female	18/20 (90.0)	47/ 51 (92.2)
Race		
White	124/134 (92.5)	254/270 (94.1)
Black	12/13 (92.3)	18/20 (90.0)
Asian	0/0 (--)	4/5 (80.0)
Other[a]	1/1 (100)	0/0 (--)
Hispanic/Latino		
Yes	15/16 (93.8)	25/26 (96.2)
No	122/132 (92.4)	251/269 (93.3)
Region		
North America	43/46 (93.5)	91/98 (92.9)
Europe	94/102 (92.2)	185/197 (93.9)

[a] Hawaiian/Pacific islander.
Source data: [U10-3028-01, Module 5.3.5.1, Table 15.2.1: 13]

Table 44: Study 1100.1526: Proportion of virologic response at Week 24 using LLOQ=50 copies/mL by baseline characteristics (Amplicor-corrected, TLOVR algorithm)

	Number with response/total number (%)	
Baseline characteristics	**NVP IR 200 BID**	**NVP XR 400 QD**
Total number of patients	137/148 (92.6)	276/295 (93.6)
Background therapy (N[%])		
Truvada®	77/82 (93.9)	145/158 (91.8)
Combivir®	29/30 (96.7)	59/63 (93.7)
Kivexa® / Epzicom™	31/36 (86.1)	72/74 (97.3)
Baseline CD4+ count (cells/mm^3) (N [%])		
>50 - 200	2/2 (100)	6/6 (100)
>200 - 350	11/17 (64.7)	40/43 (93.0)
>350 - <400	11/12 (91.7)	21/23 (91.3)
≥400	112/116 (96.6)	209/223 (93.7)
Missing	1/1 (100.0)	0/0 (--)
CDC class (N [%])		
Non-AIDS (A1, A2, B1, B2)	93/97 (95.9)	163/174 (93.7)
AIDS (A3, B3)	20/26 (76.9)	60/65 (92.3)
AIDS (C1, C2, C3)	24/25 (96.0)	53/56 (94.6)
Baseline HIV-1 RNA (copies/mL) (N [%])		
<50	127/136 (93.4)	264/280 (94.3)
≥50	10/12 (83.3)	12/15 (80.0)
NVP as the first HAART regimen (N [%])		
Yes	67/73 (91.8)	125/134 (93.3)
No	70/75 (93.3)	151/161 (93.8)
Duration of previous NVP IR treatment [N (%)]		
<1 year	27/30 (90.0)	49/52 (94.2)
1-3 years	38/44 (86.4)	94/101 (93.1)
3-5 years	34/35 (97.1)	70/75 (93.3)
>5 years	38/39 (97.4)	63/67 (94.0)
Type of previous background therapy prior to study medication [N (%)]		
PI based	26/28 (92.9)	57/58 (98.3)
NNRTI based	8/8 (100.0)	21/23 (91.3)
PI based and NNRTI based	11/11 (100.0)	23/27 (85.2)
NRTI[a]	25/28 (89.3)	50/53 (94.3)

[a] Previous regimens were NRTI only (abacavir [ABC], lamivudine [3TC], and zidovudine [ZDV]) or included ABC, 3TC, and ZDV as part of the background.
Source data: [U10-3028-01, Module 5.3.5.1, Table 15.2.1: 15]

Virologic response and trough plasma concentrations

The effect of trough concentrations on the sustained virologic response at Week 24 was evaluated using gMean trough level, which was defined as the geometric mean of all available steady-state

troughs from Week 2 to Week 24 for each patient. There were no race or gender interactions with minimum steady-state trough levels.

Study 1100.1518: An open-label, multiple dose, cross-over study to evaluate the steady state pharmacokinetic parameters of nevirapine extended release tablets in HIV-1 infected children, with an optional extension phase (Phase I)

Study 1100.1518 is an open-label, multiple dose, cross-over study to evaluate the steady-state pharmacokinetic (PK) parameters of nevirapine extended release tablets in HIV-1 infected children 3 to <18 years of age who had been treated for at least 18 weeks with a nevirapine IR based regimen without protease inhibitors and had a screening viral load (VL) <50 copies/ml. Patients remained on their previous background antiretroviral regimen and were treated with Viramune (nevirapine IR) for a 10-day run-in phase, after which nevirapine XR was administrated once daily for 10 days for PK evaluation.

Objectives

The primary objective of the study was to establish the pharmacokinetic profile at steady state of nevirapine XR in children 3 to <18 years of age by obtaining morning trough (pre-dose) plasma and/or saliva concentrations in all patients during the PK evaluation phase of the study as well as serial PK samples from a subset of patients. Efficacy was evaluated by the proportion of patients maintaining a viral load <50 copies/mL at the end of the PK evaluation (Day 22).

Blinding (masking)

Open label trial design

Statistical methods

Descriptive analysis

Results

Baseline data

A total of 85 patients were entered into the study having been treated with a nevirapine IR based regimen for at least 18 weeks. The majority of patients, 83.5%, had been on a nevirapine IR based regimen for 2 or more years. Either AZT or D4T plus 3TC were the main NRTI background therapies patients taken (87.1%). Patients belonged to the following age categories: 26 patients were 3 to <6 years old, 26 patients were 6 to <12 years old and 33 patients were 12 to <18 years old.

Overall, 55.3% of the patients were female; 92.9% were black due to the fact that the majority of subjects were enrolled in South Africa and Botswana.

Key baseline characteristics relative to HIV-1 disease showed that the majority of patients, 87.1%, had baseline CD4+ cell counts greater than 500 cells/mm3 and all of the patients with known cell counts had counts greater than 200 cells/mm3. Most patients, 90.6%, had baseline CD4+ cell percentage greater than 25%.

The following table summarizes relevant demographic data.

Table 45: Demographics in Study 1100.1518

	3 - <6 yr	6 - <12 yr	12 - <18 yr	Total
Number of patients	26 (100.0)	26 (100.0)	33 (100.0)	85 (100.0)
Gender [N (%)]				
Male	13 (50.0)	12 (46.2)	13 (39.4)	38 (44.7)
Female	13 (50.0)	14 (53.8)	20 (60.6)	47 (55.3)
Race [N (%)]				
Black	25 (96.2)	22 (84.6)	32 (97.0)	79 (92.9)
White	1 (3.8)	4 (15.4)	1 (3.0)	6 (7.1)
Hispanic/Latino [N (%)]				
No	26 (100.0)	25 (96.2)	33 (100.0)	84 (98.8)
Yes	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.2)
Region [N (%)]				
North America	0 (0.0)	0 (0.0)	2 (6.1)	2 (2.4)
Africa	22 (84.6)	20 (76.9)	29 (87.9)	71 (83.5)
Europe	4 (15.4)	6 (23.1)	2 (6.1)	12 (14.1)

Source data: [U10-3350-01, Module 5.3.3.2, Table 15.1.4: 1]

Outcomes and estimation

The HIV-1 viral load and CD4+ cell count and percentage were measured at baseline, Visit 3 (Day 11, end of nevirapine IR PK run-in phase), and Visit 7 (Day 22, immediately after the nevirapine XR PK phase). The proportions of patients with viral load < 50 copies/ml by visit are summarized in Table 46.

Table 46: Proportion of patients in Study 1100.1518 with viral load < 50 copies/mL by visit - FAS

	No. of patients with viral load < 50 copies/mL / total no. (%)				
		NVP XR			
Visit Day	NVP IR	XR 200QD	XR 300QD	XR 400QD	Total
Baseline*	83 / 85 (97.6)	-	-	-	83 / 85 (97.6)
Day 11 / Visit 3	77 / 83 (92.8)	-	-	-	77 / 83 (92.8)
Day 22 / Visit 7	-	35 / 35 (100.0)	19 / 20 (95.0)	24 / 24 (100.0)	78 / 79** (98.7)

* Baseline was the geometric mean of viral load measurements from the most recent two measurements before trial medicine was taken.

** In addition to 5 patients who discontinued before Visit 7, one patient (# 10227) had no VL measurement at Visit 7.

Source data: [U10-3350-01, Module 5.3.3.2, Table 15.2.1: 1]

Most measurements of VL > 50 copies/ml were isolated and therefore considered "blips" (Table 2.3: 3). The highest VL measurement was 239 copies/ml in one patient. Viral load measurements from this patient returned to VL < 50 copies/ml in subsequent visits.

No patients met criteria for virologic failure as defined by two consecutive measurements of VL > 50 copies/ml.

Geometric mean steady-state nevirapine XR pre-dose trough concentrations (Cpre,ss) were 3880 ng/ml, 3310 ng/ml and 5350 ng/ml in age groups 3 to <6 years, 6 to <12 years, and 12 to <18 years of age, respectively.

Clinical studies in special populations

Special populations were not addressed in the clinical separate studies except for children. Please refer to the relevant points.

In Study 1100.1486, analyses of subpopulations revealed that no relationship was observed between age group, gender, race, ethnicity or region and sustained virologic response at Week 48 for the two treatment groups.

In Study 1100.1526, analyses of subpopulations revealed that no relationship was observed between age group, gender, race, ethnicity or region and sustained virologic response at Week 24 for the two treatment groups.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 47: Summary of Efficacy for Trial 1100.1486

Title: A randomised, double blind, double dummy, parallel group, active controlled trial to evaluate the antiviral efficacy of 400 mg QD ne**V**irapine **E**xtended **R**elease formulation in comparison to 200 mg BID ne**V**irapin**E** immediate release in combination with Truvada® in antiretroviral therapy naïve HIV-1 infected patients (**VER*x*VE)**			
Study identifier	2007-003654-29		
Design	Eligible patients were stratified by their baseline HIV-1 viral load (defined as the maximum of screening viral load or Day 0 viral load) to ≤100,000 copies/mL or >100,000 copies/mL strata. Within each stratum, they were randomised to receive 400 mg QD nevirapine XR or 200 mg BID nevirapine IR, after a 14-day lead-in period in which all the patients received 200 mg QD nevirapine IR formulation. Background ARV therapy was Truvada® (emtricitabine and tenofovir disoproxil fumarate) QD in both treatment groups. Treatment duration for the primary endpoint was 48 weeks with an extension through 144 weeks. Efficacy, safety, and pharmacokinetic (PK) parameters were evaluated at each study visit. An optional pharmacokinetic substudy included intensive PK blood collection on Day 28.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks 14 days 144 weeks
Hypothesis	Non-inferiority (NI): This study was powered (90%) to demonstrate non-inferiority of the nevirapine XR formulation to the nevirapine IR formulation with regard to the proportion of sustained virologic response at Week 48 using -10% NI margin.		
Treatments groups	Nevirapine XR		Nevirapine XR tablet 400 mg QD, at least 48 weeks, 505 patients randomized
	Nevirapine IR		Nevirapine IR tablet 200 mg BID, at least 48 weeks, 508 patients randomized
Endpoints and definitions	Primary Endpoint	Sustained virologic response at Week 48	A virologic response was defined by two consecutive measurements of VL <50 copies/mL, at least two weeks apart. A sustained virologic response had no virologic rebound or change of ARV therapy through Week 48.
	Key Secondary Endpoint	Time to loss of virologic response	The time between the start of the lead-in period and the last VL <50 copies/mL in a patient who initially had virologic response prior to Week 48 but subsequently demonstrated virologic rebound prior to the time when the last enrolled patient was on treatment for 48 weeks. Patients who did not achieve VL <50 copies/mL by Week 48 were defined as having a time of loss of virologic response of zero.
Database lock	December 3, 2009		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) This was a subset of the treated set that included all randomized patients who took at least one dose of randomized (blinded) investigational treatment. This subset excluded patients who took open-label lead-in nevirapine IR QD, but dropped out prior to randomization or prior to taking the first dose of randomized (blinded) nevirapine XR or nevirapine IR after randomization. Week 48 analysis.		
Descriptive statistics and estimate variability	Treatment Group	NVP IR 200 BID	NVP XR 400 QD
	Number of subjects	506	505
	Proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)	384/506 (75.9%)	409/505 (81.0%)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Difference in proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)
		Cochran's statistic (difference in percentage)	4.9%
		95% CI	(-0.1%, 10.0%)
		P-value	<0.0001
Analysis description	**Secondary analysis for the primary endpoint**		
Analysis population and time point description	Full Analysis Set (FAS) This was a subset of the treated set that included all randomized patients who took at least one dose of randomized (blinded) investigational treatment. This subset excluded patients who took open-label lead-in nevirapine IR QD, but dropped out prior to randomization or prior to taking the first dose of randomized (blinded) nevirapine XR or nevirapine IR after randomization. Week 48 analysis.		
Descriptive statistics and estimate variability	Treatment Group	NVP IR 200 BID	NVP XR 400 QD
	Number of subjects	506	505

	Proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (TaqMan-only, TLOVR algorithm)	368/506 (72.7%)	386/505 (76.4%)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Difference in proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)
		Cochran's statistic (difference in percentage)	3.5%
		95% CI	(-1.8%, 8.8%)
		P-value	<0.0001

Table 48: Summary of Efficacy for Trial 1100.1526

Title: 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			
Study identifier	2008-004681-55		
Design	Open label, randomized, parallel group study. After screening, patients were randomised with a 2:1 allocation ratio to nevirapine XR 400 mg QD or nevirapine IR 200 mg BID. Patients remained on their previous background therapy. Treatment duration was 48 weeks. The randomisaon at baseline was stratified by background therapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks There was no run-in phase 144 weeks	
Hypothesis	Non-inferiority (NI): Proportions of sustained virologic response through Week 24 were estimated for both treatments using the TLOVR algorithm and SNAPSHOT approach. A non-inferiority test (Δ = 12%, 10%) was performed by constructing a two-sided 95% CI for the difference in the proportions of virologic response between nevirapine XR and nevirapine IR treatment groups for the primary endpoint.		
Treatments groups	Nevirapine XR	Nevirapine XR tablet 400 mg QD, at least 24 weeks, 296 patients randomized	
	Nevirapine IR	Nevirapine IR tablet 200 mg BID, at least 24 weeks,149 patients randomized	
Endpoints and definitions	Primary Endpoint	Sustained virologic response (viral load<50 copies mL) at Week 24	Proportion of patients with sustained virologic response (viral load<50 copies mL) through Week 24. A patient was considered as a treatment failure at the earliest time of any one of the following events prior to Week 24: A virologic failure defined by viral load ≥50 copies/mL measured at two consecutive visits, at least two weeks apart; Changed ARV therapy; Death; Lost to follow up

	Secondary Endpoint	Sustained virologic response (viral load<400 copies mL) at Week 24	Proportion of patients with sustained virologic response (viral load<400 copies mL) through Week 24. A patient was considered as a treatment failure at the earliest time of any one of the following events prior to Week 24: A virologic failure defined by viral load ≥400 copies/mL measured at two consecutive visits, at least two weeks apart; Changed ARV therapy; Death; Lost to follow up
	Secondary Endpoint	Time to loss of virologic response	The time between the start of the lead-in period and the last VL <50 copies/mL in a patient who initially had a virologic response prior to Week 48 but subsequently demonstrated virologic rebound prior to the time when the last enrolled patient was on treatment for 48 weeks. Patients who did not achieve VL <50 copies/mL by Week 48 were defined as having a time of loss of virologic response of zero.
Database lock	September 3, 2009		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. This set is the same as the treated set. Week 24 analysis.		
Descriptive statistics and estimate variability	Treatment Group	NVP IR 200 BID	NVP XR 400 QD
	Number of subjects	148	295
	Proportion of virologic response at Week 24 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)	137/148 (92.6%)	276/295 (93.6%)

Effect estimate per comparison	Primary Endpoint	Comparison groups	Difference in proportion of virologic response at Week 24 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)
		Cochran's statistic (difference in percentage)	1.0%
		95% CI	(-4.3%, 6.2%)
		P-value	<0.025

Analysis description	**Secondary analysis for the primary endpoint**		
Analysis population and time point description	Full Analysis Set (FAS) This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. This set is the same as the treated set. Week 24 analysis.		
Descriptive statistics and estimate variability	Treatment Group	NVP IR 200 BID	NVP XR 400 QD
	Number of subjects	148	295
	Proportion of virologic response at Week 24 using LLOQ = 50 copies/mL (TaqMan-only, TLOVR algorithm)	133/148 (89.9%)	269/295 (91.2%)

Effect estimate per comparison	Primary Endpoint	Comparison groups	Difference in Proportion of virologic response at Week 48 using LLOQ = 50 copies/mL (Amplicor-corrected, TLOVR algorithm)
		Cochran's statistic (difference in percentage)	1.3%
		95% CI	(-4.7%, 7.3%)
		P-value	<0.025

Table 49: Summary of Efficacy for Trial 1100.1518

Title: An open-label, multiple dose, cross-over study to evaluate the steady-state pharmacokinetic parameters of nevirapine extended release tablets in HIV-1 infected children, with an optional extension phase		
Study identifier	2008-005855-61	
Design	An open-label, multiple dose, cross-over study to evaluate the steady-state pharmacokinetic parameters of nevirapine extended release tablets in HIV-1 infected children, with an optional extension phase. Patients remained on their present background therepy. Treatment duration was 22 days followed by an optional extension phase.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	10 days 11 days Until the IND is withdrawn, the drug is commercailly available or an expanded access is set up.
Hypothesis	No hypothesis testing planned.	

Treatments Groups	Nevirapine IR/XR		This was a multiple-dose study in which children from 3 to <18 years old were treated with NVP IR for an 11-day run-in phase including a baseline PK evaluation, followed by NVP XR for 10 days at doses of 200 mg (100 mg x 2 tablets), 300 mg (100 mg x 3 tablets), or 400 mg (1 tablet), depending on body weight (BW) or body surface area (BSA; 300 mg/m^2 per day). NVP XR dosing was based on the previous NVP IR dose which patients received during the run-in phase as follows: 175-249 mg/day of IR was 200 mg XR equivalent, 250-349 mg/day of IR was 300 mg XR equivalent and ≥350 mg/day of IR was 400 mg XR equivalent.
Endpoints and definitions	Primary Endpoint	PK parameter:Trough $C_{pre, N}$	Trough drug concentration immediately prior to the next scheduled dose
	Secondary Endpoint	Other PK parameters	$C_{max,ss}$ /$C_{min,ss}$, %PTF, $t_{max,ss}$, CL/F_{ss}, C_{avg}, $AUC_{\tau,ss}$, $C_{min,ss}$, and $C_{max,ss}$ (at least 32 patients)
	Secondary Endpoint (efficacy)	Viral load measurement	Proportion of patients maintaining a viral load < 50 copies/mL at Day 22 (and at Week 24 during the OEP)
Database lock	February 5, 2010		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. 22 Day PK analysis.			
Descriptive statistics and estimate variability	Treatment Groups	NVP XR 200 QD	NVP XR 300 QD	NVP XR 400 QD
	Number of subjects	34	20	20
	Pre-dose nevirapine steady-state trough concentrations (XR, Day 21) Mean (CV%)	4120 (67.0%)	5760 (56.3%)	5170 (45.6%)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Descriptive statistics, no comparison	

Analysis description	Secondary efficacy endpoint			
Analysis population and time point description	Full Analysis Set (FAS) This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. It is same as treated set. 22 Day PK analysis.			
Descriptive statistics and estimate variability	Age groups	3-<6 years	6-<12 years	12-<18 years
	Number of subjects	26	26	33
	Proportion of patients with viral load <50 copies/mL on Day 22 (at the end of PK XR treatment)	24/25 (96.0)	23/23 (100.0)	31/31 (100.0)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Descriptive statistics, no comparison	

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The characteristics and number of study participants are adequate for the proposed objectives in each study, taking in consideration that these clinical trials should be regarded as bridging studies in order to support an application to extend the Marketing Authorisation. Overall, the demographic and baseline characteristics were similar between the two treatment groups for both studies (1100.1486 and 1100.1526).

The Study objectives were in line with the proposed methodology. The randomisation methodology is adequately described for the presented studies. Only study 1100.1486 is double blind. Studies 1100.1526 and 1100.1518 are open label studies. Although ideally all the studies should be blinded, the primary variables are based on laboratory determinations reducing potential bias.

The statistical methods and performed analysis were adequate in the trials.

According to the sample size determination mentioned in the protocol of the study 1100.1526, it was planned to randomise 200 patients in the nevirapine XR arm and 100 patients in the nevirapine IR arm. The applicant has nevertheless judged necessary to increase the sample size leading to enrol 296 patients in the nevirapine XR arm and 149 in the in the nevirapine IR arm.

As patients could have dropped out of the studies before they reached the planned observation time, various methods were used to assess the impact of missing data on the efficacy endpoints of the studies. In particular, patients with a lack of efficacy would be expected to drop out with a higher probability than patients showing a good response. In study 1100.1486 the most frequent reason for discontinuation prior to 48 weeks was AE occurrence in 7.3% of all patients (8.3% patients in the nevirapine IR group and 6.3% patients in the nevirapine XR group), followed by lack of efficacy in 4.9% of all patients (5.1% patients in the nevirapine IR group and 4.8% patients in the nevirapine XR group). The reason for discontinuation due to lack of efficacy was based on the investigator's

assessment. As it is a double blind study, the risk of bias introduced by the investigator's judgment could be considered acceptable. In general, the frequency of premature discontinuation was comparable between the two treatment groups, with the exception of 6 pregnancies, which all occurred in the nevirapine XR group. No conclusions can be derived from these figures in pregnant women as one case occurred during the Lead in phase and only one pregnancy was treated with NVP IR. In Study 1100.1526, the most frequent reason for discontinuation prior to 24 weeks was AE occurrence for 3 patients in the nevirapine XR group, followed by lost to follow up for 2 patients (1 in each treatment group) and noncompliance (2 patients in the nevirapine XR group).

It would have been appropriate to perform a sensitivity analysis to take into account missing data at week 48 due to a premature discontinuation of treatment, all the more that the number of treatment discontinuation is somewhat more important in the nevirapine IR arm than in the XR arm (92 vs 80).

Due to NVP XR dosing schedule (once a day) it was expected that compliance would be better for the XR than in IR group. In general, the frequency of premature discontinuation was comparable between the two treatment groups.

Efficacy data and additional analyses

The MAH presented a short clinical programme in order to support the Extension Application for three new formulations (Nevirapine prolonged-release tablets 400 mg, 100 mg and 50 mg).

In addition to PK/PD studies, three clinical studies were presented.

The efficacy data showed that the XR formulation was not inferior to the IR presentations. For some of the evaluated variables there was a trend in favour of the XR tablets. One of the potential advantages of the once a day regimen is the better compliance. This was however not shown in the provided clinical studies. Nevertheless, this could perhaps be explained by the "controlled" environment in clinical trials.

The presented clinical programme should be regarded as a bridging programme towards the new prolonged-release forms since it would be insufficient on its own to support the nevirapine indication on HIV infection treatment.

Study 1100.1486

Since the pre-specified non-inferiority margin was -10%, the -0.1% lower bound demonstrated the non-inferiority of nevirapine XR to nevirapine IR treatment (p-value <0.0001 for the non-inferiority test). The results of the secondary analyses of the primary endpoint also support the non-inferiority of nevirapine XR to nevirapine IR, according to the pre-specified –10% non-inferiority margin.

The analysis of the secondary endpoints supports the findings on the main endpoint.

For trough concentrations above 1 µg/ml, there appeared to be no effect of the nevirapine trough level on the proportion of virologic responders when using the gMean trough level. Patients in the 1 to<2 µg/ml trough group had comparable virologic response rates with those in the ≥2 µg/ml trough groups. These findings were consistent when the minimum steady-state nevirapine trough from Week 4 to Week 48 for each patient was used as the trough level.

For nevirapine XR, the 10th percentile trough concentrations were all above 1,800 ng/ml (Week 4 to Week 48). This concentration was at least 13.4-fold higher than the concentration necessary to inhibit 90% of viral replication (IC90) for wild type HIV-1 virus. The CHMP agrees on that the concentration results, along with the efficacy results, suggesting that treatment with nevirapine XR 400 mg QD was effective even though lower nevirapine exposures were observed compared with those for nevirapine IR treatment.

Study 1100.1526

Primary endpoint analysis demonstrated the non-inferiority of nevirapine XR to nevirapine IR treatment.

Results from all of the secondary analyses of the primary endpoint also demonstrate the non-inferiority of nevirapine XR to nevirapine IR treatment, based on the pre-specified -12% non-inferiority margin and the more stringent -10% non-inferiority margin.

There was a small difference on CD4+ cell counts in favour of NVP IR group (see table below) that is probably not clinically relevant.

Table 50: Change from baseline in CD4+ count (cells/mm^3) at Week 24, Study 1100.1526 - FAS

		NVP IR 200 BID		NVP XR 400 QD	
Analysis type	**Visit Week**	**N**	**LS Mean[a] (SE)**	**N**	**LS Mean[a] (SE)**
Observed values	Week 24	142	50.7 (12.7)	282	46.1 (9.2)
LOCF	Week 24	147	50.3 (12.3)	292	45.3 (8.9)

[a] The least square mean was based on the ANCOVA model, adjusted for background ARV therapy stratum.
Source data: [U10-3028-01, Module 5.3.5.1, Table 15.2.3: 2, Appendix 16.1.9.2, Statdoc 6.3.1]

There was no trough effect found on the proportion of virologic responders for either treatment group.

Subgroup analysis (Study 1100.1486 and Study 1100.1526)

For Study 1100.1486, there appeared to be no relationship between the proportion of sustained virologic response at Week 48 and any baseline demographic characteristic (age group, gender, race, ethnicity and region) or other baseline characteristic (CD4+ cell count, HIV-1 sub-type, CDC class, and lead-in duration). Descriptive statistics showed that patients with a baseline HIV-1 viral load ≤100,000 copies/ml had a higher proportion of sustained virologic response at Week 48 (79.2% in the nevirapine IR and 85.9% in the nevirapine XR group) than those with >100,000 copies/ml (70.9% in the nevirapine IR and 73.2% in the nevirapine XR group). For each viral load stratum, the nevirapine XR group had a higher proportion of virologic responders than the nevirapine IR group.

For Study 1100.1526 there was no apparent relationship between the proportion of sustained virologic response at Week 24 and any baseline demographic characteristic (age group, gender, race, ethnicity and region) or baseline characteristic, including type of background therapy received, nevirapine as the first HAART regimen, duration of previous nevirapine IR treatment, and type of previous background therapy prior to study medication. Nevertheless a trend to more favorable results on XR group was found in patients on Kivexa/Epzicom background therapy (86.1% in the nevirapine IR and 97.3 % in the nevirapine XR group).

Virological resistance

Based on the analyses for the 86 resistance testing patients, the observed mutations were those that would be expected with a nevirapine-based regimen according to the current nevirapine label and the IAS list of nevirapine-associated mutations. Two new amino acid substitutions were identified as being associated with nevirapine failure and phenotypic resistance to nevirapine in this study: Y181I and Y188N. No difference in resistance related to the formulation type (nevirapine IR and nevirapine XR)

was observed. Thus, XR formulation does not appear to induce virological resistance in excess when compared to IR formulation.

Study 1100.1518

The main study conclusions are endorsed as the administration of nevirapine XR once daily formulation either as 2 or 3 tablets of 100 mg strength or 1 tablet of 400 mg strength achieved the target trough concentrations across doses and age groups, which have been demonstrated to be effective in adults. These trough concentrations are above a pre-established target concentration of approximately 3,000 ng/ml with a once-daily dosing regimen.

Viral load suppression during the short duration of dosing with neviraine XR in this PK study was maintained. Overall, nevirapine XR was safe and well tolerated in patients 3 years of age or older who were able to swallow tablets.

2.5.3. Conclusions on the clinical efficacy

The efficacy of nevirapine prolonged-release tablet is considered non-inferior to that of nevirapine IR tablet in both treatment-naïve and treatment–experienced (switch) HIV-1 infected patients. For paediatric patients, study 1100.1518 demonstrates that the 100 mg nevirapine XR dose increment is appropriate and provides adequate dose adjustment for paediatric patients switching from twice daily nevirapine IR to once daily XR dosage forms.

2.6. Clinical safety

Patient exposure

The overall extent of exposure for nevirapine XR was 1,265 subjects. This included 1,182 adults and 83 children.

In Phase I studies, single doses of nevirapine XR prototypes were received by 242 male volunteers; and nevirapine XR prototypes were administered for 21 days to 92 patients. Forty-eight male volunteers received single doses of nevirapine XR in a Phase I bioequivalence study.

There were 85 children enrolled in a multiple-dose 10-day Phase I pharmacokinetic study. There were 83 children exposed to nevirapine XR. The mean duration of exposure was 10 days, and most children were exposed for at least 7 days.

In Phase III studies, 800 patients received the final 400 mg nevirapine XR formulation proposed for registration, 736 patients for at least 24 weeks, 423 patients for at least 48 weeks, and 165 patients for at least 72 weeks

Adverse events

Phase I studies

The nevirapine XR safety data reported in 3 short-term exposure clinical studies (treatment duration 1 to 21 days; Study 1100.1485, Study 1100.1489, and Study 1100.1517) did not reveal any new or unexpected safety issue and were consistent with the list of side effects expected with nevirapine IR as described in the labeling. These studies (Study 1100.1485, Study 1100.1489) were conducted to test and select the formulation and dose of the nevirapine XR formulation for further development. As no obvious safety signals arose, the clinical program progressed to Phase III.

Additional Phase I studies were performed in support of the paediatric indication (Study 1100.1531 and Study 1100.1518). No safety issues arose in these studies.

Single-dose studies in healthy volunteers

Across the single-dose PK studies, no deaths occurred, there were 2 SAEs reported, and 2 subjects discontinued due to adverse events. The investigator-defined drug-related AEs were generally mild or moderate in intensity. One subject had a mild drug-related rash during treatment with nevirapine IR. No obvious dose or formulation relationships with AE rates were observed. The single-dose Phase I studies demonstrated adequate safety and tolerability to proceed with the clinical evaluation of selected nevirapine XR prototypes in Study 1100.1489 and Study 1100.1518.

Study 1100.1489 - multiple-dose PK study in HIV+ patients (n = 92)

One subject experienced an SAE (moderate hypoacusis), but this SAE was not considered related to drug. No subjects experienced severe or life-threatening AEs and no subjects experienced AEs that led to discontinuation of study treatment. No subjects died during the study. Twenty-four (26.1%) of the 92 patients reported at least 1 AE during the (baseline) nevirapine IR period. During treatment with nevirapine XR, the incidence of AEs ranged from 28.6% in subjects in the nevirapine XR 300 mg HPMC 25% group to 58.3% in the nevirapine XR 400 mg HPMC 25% group. All AEs were categorized as DAIDS Grade 1 (mild) or Grade 2 (moderate). The most frequently reported SOCs were Infections and Infestations (24 subjects), followed by Gastrointestinal Disorders (15 subjects), and Nervous System Disorders (14 subjects). The most frequently reported preferred term was nasopharyngitis (10 subjects). AEs considered related to the study drug were reported in 6 subjects.

Study 1100.1518 - Multiple-dose PK study in HIV-1 infected children (IR, n = 85; XR, n = 83)

There were no deaths and no SAEs during the nevirapine IR or XR treatment period. One subject discontinued for an SAE in the post-treatment phase. This event was not considered by the investigator to be drug-related. No patient discontinued due to an adverse event. There were no Grade 4 adverse events. There was one patient with Grade 3 pyrexia; however, the pyrexia was categorized as unrelated to study drug by the Investigator.

The percentage of patients who experienced at least one adverse event was 28.2% (24/85) in the IR treatment phase and 47.0% (39/83) of patients in the XR treatment phase. The difference between the percentage of patients reporting adverse events in the IR and XR treatment periods was largely due to the increased number of infections during the XR treatment period. None of these infections were considered related to study drug.

The most frequently reported AEs by system organ class were infections and infestations (IR, 8/85 patients, 9.4%; XR, 20/83 patients, 24.1%), skin and subcutaneous tissue disorders (IR, 5/85 patients, 5.9%; XR, 9/83 patients, 10.8%) and respiratory disorders (IR, 9/85 patients, 10.6%; XR, 5/83 patients, 6.0%). The frequency of reported AEs by system organ class was similar among the three age groups during the nevirapine IR run-in and nevirapine XR phases.

There were 10 patients during each treatment phase who experienced AEs considered by the investigator to be related to the study drug (IR, 10/85 patients, 11.8%, XR, 10/83 patients, 12%). The most frequent AEs considered by the investigator to be possibly drug-related were headache (IR, 4/85 patients, 4.7%; XR 1/83 patients, 1.2%) and rash (IR 4/85 patients, 4.7%; XR 7/83 patients, 8.4%].

There were 7 subjects with drug-related rash during the XR treatment phase or within 10 days of the last dose of XR. Although these patients had rashes that were considered possibly related to nevirapine by the investigator, all of the events occurred in patients after more than 18 weeks of nevirapine IR treatment (usual time-frame of nevirapine-related occurrences). Further, all but 1 of the patients with

a rash were from the same study site, in a community which had experienced an outbreak of measles. There were no concomitant increases in LFTs. Most events were rated as mild, and no patient discontinued nevirapine due to the events. This information supports that the clinical likelihood of these events being related to nevirapine is low.

Phase III studies

The AE data were presented separately for the two Phase III studies due to major differences in: study design (double-blind, double-dummy [Study 1100.1486] vs. open-label [Study 1100.1526]), patient populations (HIV-1 treatment-naïve patients [Study 1100.1486] versus patients already on nevirapine IR treatment [Study 1100.1526]) and primary endpoint study duration (48 weeks [Study 1100.1486] vs. 24 weeks [Study 1100.1526]). Also, for Study 1100.1486, AE data were presented separately for the two-week lead-in phase
(pre-randomisation, all patients on nevirapine IR 200 mg once-daily (as recommended in the current nevirapine IR label) and the randomised phase (nevirapine XR 400 mg once-daily vs. IR 200 mg twice-daily).

Study 1100.1486 - lead-in phase

Of the 1068 patients treated with at least one dose of 200 mg nevirapine IR during the lead-in phase (treated set), 465 (43.5%) reported at least one AE, 210 patients (19.7% of the total population) a drug-related AE (according to the investigator), and 45 (4.2%) an AE leading to (temporary) discontinuation of study drug (7 of these restarted treatment and went on into randomisation; 38 [3.6%] did not continue into the randomized phase). Overall, 55 patients (5.1%) were not randomized.

Twenty patients (1.9%) reported an SAE during the lead-in phase (among those patients, 7 each were reported in the SOCs Infections and Infestations and Skin and Subcutaneous Tissue). The main reason for the "Seriousness" criterion was hospitalization. No deaths were reported during the lead-in phase.

Patients reported 317 (29.7%) AEs of mild intensity (DAIDS Grade 1); 118 (11.0%), 28 (2.6%) and 2 (0.2%) patients reported AEs of moderate (Grade 2), severe (Grade 3), and potentially life-threatening (Grade 4) intensity, respectively.

Among the AEs reported during the lead-in phase, the most frequent were rash (79 [7.4%]), nausea (68 [6.4%]), headache (57 [5.3%]), fatigue (40 [3.7%]) and pyrexia (22 [2.1%]).

Most of the 55 patients not continuing to the randomisation phase reported rash (31/55) or pyrexia (14/55). AEs reported by this group were mostly DAIDS Grade 2 or 3. Two cases of Steven-Johnson syndrome (0.2%) were reported during the lead-in phase.

Hepatic events were reported by 5 [0.5%] patients during the lead-in phase, and 3 of these patients were not randomized. Those 3 patients had multiple symptoms specific for hepatitis and reported hypersensitivity reactions. No patients experienced asymptomatic transaminase elevations.

Study 1100.1486 - randomised phase

Of the 1011 patients treated with at least one blinded dose of either nevirapine XR (n = 505) or nevirapine IR (n = 506) during the double-blind randomised phase (full analysis set) until data cut-off date, 895 (88.5%) reported at least one AE (XR: 443 [87.7%], IR: 452 [89.3%]). Of these, for 223 patients (22.1% of the FAS population) an investigator-rated drug-related AE was reported (XR: 100 [19.8%], IR: 123 [24.3%]). In 77 (7.6%) patients, an AE lead to discontinuation of study drug (XR: 32 [6.3%], IR: 45 [8.9%]). Six deaths (0.6%) were observed, 1 (0.2%) in the XR group and 5 (1.0%) in the IR group (two of these after Week 48). None were considered related to the study treatment.

The AE pattern observed during the double-blind phase of Study 1100.1486 was consistent with the previously known safety and tolerability profile of nevirapine IR. A consistent trend was observed towards lower incidences in favour of nevirapine XR vs. nevirapine IR for:

- AEs leading to discontinuation (6.3% vs. 8.9%),
- AEs considered drug-related by the investigator (19.8% vs. 24.3%),
- Hepatic events (5.5% vs. 9.1%) and symptomatic hepatic events (1.6% vs. 2.8%)
- DAIDS Grade 3 and 4 AEs (14.5% vs. 18.0%), and
- Deaths (0.2% [1/505] vs. 1.0% [5/506]).

Study 1100.1526

Of the 443 patients treated with at least one dose post-randomisation of either nevirapine XR (n = 295) or nevirapine IR (n = 148), 312 (70.4%) reported at least one AE (XR: 223 [75.6%], IR: 89 [60.1%]). Of these, for 38 (8.6% of the FAS population) an investigator-rated drug-related AE was reported (XR: 35 [11.9%], IR 3 [2.0%]). In 3 (1.0%) patients randomized to XR, an AE lead to discontinuation of study drug (no patients on IR discontinued due to an AE). No deaths were observed in Study 1100.1526 during the observation period covered by this safety analysis.

In this open-label study, there were higher rates of AEs reported in those changing to investigational therapy with nevirapine XR compared to the rates observed in those patients continuing on their previous licensed therapy of nevirapine IR. This finding is inconsistent with the results of the double-blind study in treatment-naïve patients (Study 1100.1486). The reporting difference in AEs between treatment groups observed in Study 1100.1526 was mainly due to differences in the frequency of mild events, 35.8% with nevirapine IR vs. 49.5% with nevirapine XR. AEs identified as occurring more frequently were events in the following SOCs: Gastrointestinal disorders, Central Nervous System disorders, Psychiatric disorders, and General disorders. No notable difference in AEs between treatment groups was reported for AEs of DAIDS Grade 2 or higher.

The most likely cause for the observed difference in reported AEs between nevirapine XR and nevirapine IR in the open-label switching Study 1100.1526 is a reporting bias in favour of the previously prescribed, "familiar" treatment (in this case, nevirapine IR), and to the disadvantage of the new investigational treatment (in this case, nevirapine XR). This hypothesis is supported by results of the double-blind pivotal Phase III Study 1100.1486, which showed a favourable tolerability and safety profile of nevirapine XR compared to nevirapine IR.

Serious adverse event/deaths/other significant events

Phase I studies

Deaths

No deaths occurred in any of the Phase I studies.

Serious adverse events

Four SAEs occurred during the course of the Phase I studies: appendicitis, syphilis illness with hypoacusis, anal abscess and pneumonia. None of these events was considered related to the study drug.

Adverse events leading to discontinuations

In Study 1100.1484, 2 subjects discontinued due to adverse events (fracture of ankle and thrombocytopenia).

Phase III studies

Deaths - Study 1100.1486

Ten deaths occurred in this study. Four patients died from events that started during screening and prior to receipt of any medication, 5 patients died from events that occurred during randomized treatment, and 1 patient died from an event that started after stopping the study medication. Four patients died in the nevirapine IR treatment group and 1 patient died in the nevirapine XR group, none related to study medication.

Deaths - Study 1100.1526

No deaths occurred in this study.

SAEs (except those leading to death)

In Study 1100.1486, a total of 20 (1.9%) patients with SAEs were reported during the lead-in phase, 9 of which continued into the randomized phase. After randomization, SAEs were observed in 58 patients (11.5%) in the nevirapine XR group and in 54 patients (10.7%) in the nevirapine IR group. The most frequently reported SOC as an SAE was Infections and Infestations with an incidence of 4.1% (41/1011). Overall, the most frequently reported SAEs were pneumonia, depression, and Kaposi's sarcoma, each reported in ≤3 patients in either treatment group.

In Study 1100.1526, SAEs were reported in 21 (4.7%) patients (17/295 [5.8%] in the nevirapine XR group and 4/148 [2.7%] in the IR group), across a variety of SOCs. No SAE was considered related to study drug by the investigator or the sponsor.

Adverse events leading to discontinuations

In Study 1100.1486, 37/1068 patients (3.5%) experienced AEs during the 2-week lead-in phase that prevented continuation into the randomized phase. During the randomized phase, an AE lead to discontinuation of study drug in 77/1011 (7.6%) of patients (XR: 32 [6.3%], IR: 45 [8.9%]). The majority of patients who withdrew from the study discontinued in the first 6 weeks of the randomized phase. In Study 1100.1526, three patients (all in the XR group) experienced an AE leading to discontinuation.

Laboratory findings

Patients in nevirapine XR Phase I and III studies experienced no new lab abnormalities beyond those already associated with nevirapine. No evidence of a change in risk or new safety signal was observed with the use of either nevirapine XR or nevirapine IR. No relevant differences between nevirapine IR or XR formulations were found.

Safety in special populations

No relevant differences between nevirapine IR or XR formulations were found on special population analysis.

Adverse event analysis by gender

Gender differences for specific AEs reported in >5% of patients overall indicate that women generally reported higher frequencies of AEs than did men; only nasopharyngitis, bronchitis, and diarrhea were

reported in larger proportions of men than women. The trend of larger proportions of women reporting AEs than men was maintained when analyzed for each treatment group separately.

Women reported a lower frequency of events in the nevirapine XR group compared with women in the nevirapine IR group (any AE: XR: 60 [81.1%], IR: 71 [94.7%].

In Study 1100.1486, women reported a higher frequency of investigator-defined drug-related rash compared to men. Compared to women treated with nevirapine XR, women treated with nevirapine IR tended to report a higher number of events, although the total number of women with reported events was small. In Study 1100.1526, the AE rates observed by gender were generally consistent with those observed for the overall study population.

For female patients, hepatic events were observed more frequently in the IR group than in the XR group. 22 symptomatic events were identified, with 4 of 149 (2.7%) women affected (all in the IR group), and 18 of 862 (2.1%) men (8 in the XR group and 10 in the IR group). Grade 3/4 ALT and AST elevations were reported by 13 of 149 (8.7%) women (4-XR, 9-IR) and 54 of 862 (6.3%) men (26-XR, 28-IR). In Study 1100.1526, the AE rates observed by gender were generally consistent with those observed for the overall study population

Adverse events by treatment and race

For Study 1100.1486, adverse events reported by race exhibited similar trends to those observed for overall adverse events in all randomized patients. A slightly higher proportion of White patients reported any AE with nevirapine IR than Black patients, 91% vs. 82%, respectively.

In general, in Study 1100.1486 the proportion of White patients reporting any AEs was slightly higher in the nevirapine IR than in the nevirapine XR group (91% vs. 88%); a slightly higher proportion of Black patients reported any AE with nevirapine XR than nevirapine IR (87% vs. 82%, respectively).

Regarding Worst DAIDS severity, no meaningful differences were observed in either Study 1100.1486 or Study 1100.1526 for the occurrence of Grade 3 or 4 AEs by race.

For the AE of rash, a slightly lower proportion of blacks reported this event relative to whites; however, the numbers for rash were small.

In Study 1100.1486, the hepatic events observed among races exhibited similar trends to those reported for overall hepatic events in all randomized patients.

Pregnancy

A total of 10 pregnancies occurred during the conduct of the 2 Phase III studies.

In Study 1100.1486, one woman discontinued during the lead-in phase, and had a normal pregnancy and live birth. Eight pregnancies occurred after randomization; one was in the nevirapine IR group and seven were in the nevirapine XR group. The woman from the nevirapine IR group opted for an induced abortion. In the nevirapine XR group, one woman had a spontaneous abortion; one was still pregnant at the time of data cut-off; and 3 had a normal delivery. Two women discontinued, withdrew consent and/or were lost to follow-up, and thus delivery data were not available. No untoward effects of nevirapine were reported with any of the pregnancies or the babies. In Study 1100.1526, 1 woman discontinued from study then experienced a spontaneous abortion (miscarriage) after 4 weeks of pregnancy.

Safety related to drug-drug interactions and other interactions

No new drug interaction studies were conducted with nevirapine XR.

2.6.1. Discussion on clinical safety

The safety profile of the active pharmaceutical ingredient nevirapine has previously been established through the development and widespread use of nevirapine IR. The drug substance used in the nevirapine prolonged-release formulation is identical to that used in nevirapine IR tablets and, therefore, observed adverse events with nevirapine XR were expected to be very similar to those observed with nevirapine IR. Some expectation of a lower incidence of adverse events was hypothesized if a lower C_{max} could be achieved for the nevirapine XR formulation.

Across the four (4) single-dose PK studies in 375 healthy volunteers (Studies 1100.1484, 1100.1485, 1100.1517, and 1100.00 1531), the Phase I multiple-dose study in HIV-1 infected patients (Study 1100.1489), and the Phase I multiple-dose 10-day PK study in children (Study 1100.1518), no new or unexpected adverse events were observed. The Phase I trials demonstrated adequate safety and tolerability to proceed with the clinical development program for nevirapine XR.

In the pivotal study, Study 1100.1486 (treatment-naïve HIV-1-positive patients), 55 of 1068 patients discontinued the trial during the lead-in phase while receiving 200 mg nevirapine IR QD. Thirty-eight of these patients discontinued due to adverse events, primarily rash, consistent with the nevirapine IR label recommendations. In the randomised phase, adverse events had a numerically lower frequency in the nevirapine XR group than in the IR group as AEs summarized as "any AE" (87.7% vs. 89.3%), investigator-defined
drug-related AEs (19.8% vs. 24.3%), patients with AEs leading to study discontinuation (6.3% vs. 8.9%), and patients with DAIDS severity Grade 3 or 4 AEs (14.5% vs. 18%). A total of 6 deaths occurred after randomisation, 5 were in the nevirapine IR group and no deaths were related to study treatment.

In Study 1100.1526 (open-label trial in nevirapine treated patients), higher event rates were observed in nevirapine XR patients compared to nevirapine IR patients, respectively, as measured by proportion of patients with any AE (75.6% vs. 60.1%), investigator-defined drug-related AEs (11.9% vs. 2.0%), patients with AEs leading to study discontinuation (1.0% vs. 0%), and patients with SAEs (5.8% vs. 2.7%). However, AEs with DAIDS severity Grade 3 or 4 AEs occurred at similar rates (3.7% vs. 4.1%) in nevirapine XR and nevirapine IR groups, respectively. The applicant argues that the most likely cause for the observed difference in reported AEs between nevirapine XR and nevirapine IR in this open-label switching study is a reporting bias in favour of the previously prescribed, "familiar" treatment (nevirapine IR) and to the disadvantage of the new investigational treatment (nevirapine XR). The given explanation could be acceptable as such differences were not found in the double blind 1100.1486 study.

Rash and hepatic events were collected as AEs of special interest. In the pivotal trial, rash events occurred at a rate of 8.1% in the lead-in phase and were similar in frequency for the 2 treatment groups after randomisation, occurring in 8.3% of nevirapine XR patients and 8.7% of nevirapine IR patients. Hepatic events occurred less frequently in nevirapine XR than in nevirapine IR recipients (5.5% vs. 9.1%). This trend was consistent for events of clinical hepatitis and severe liver transaminase increases.

In Study 1100.1518, children received nevirapine IR and nevirapine XR for 10 days. There were no potentially life-threatening AEs, SAEs or AEs that led to discontinuation during the treatment phase.

One subject discontinued for an SAE in the post-treatment phase. No patient died during the study. Rash was reported by 7 patients during treatment with nevirapine XR. While these rashes were considered related to treatment by the Investigator, the occurrence of a measles outbreak made the association with study treatment uncertain. There were no unexpected clinically significant laboratory findings.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, no new AEs from those previously known to be associated with nevirapine use have been identified in the course of the studies comparing the XR and IR formulations in adults or children.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant in Module 1.8.1 of the marketing authorisation fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan (final version 1.2 adopted)

A revised RMP was provided during the procedure, detailing nevirapine drug interaction (section 1.6 of RMP). As a risk minimisation measure of granulocytopenia, a warning will be added to sections 4.4 and 4.5 of the SmPC.

TABLE 51: TABLE SUMMARY OF THE RISK MANGAMENT PLAN

Safety concern	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Important identified risk: Skin rash, including severe or life-threatening skin reactions, e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis	The incidence of these events is documented in the various clinical studies. These AEs are well characterized; the CCDS and the EU SmPC address subjects with increased risk for these events. A routine pharmacovigilance process will be used to monitor the incidence of these identified risks.	Not applicable.
Important identified risk: Severe and life-threatening hepatotoxicity incl. fatal fulminant hepatitis	The incidence of these events is documented in the various clinical studies. These AEs are well characterized; the CCDS and the EU SmPC address subjects with increased risk for these events. A routine pharmacovigilance process will be used to monitor the incidence of these identified risks.	Not applicable.

Important identified risk: Granulocytopenia, particularly in paediatric population	The incidence of these events is documented in the various clinical studies. These AEs are well characterised; the CCDS and the EU SmPC address subjects with increased risk for these events. A routine pharmacovigilance process will be used to monitor the incidence of these identified risks.	The MAH will update the sections "Special Warnings and Precautions" and "Interactions" of the EU SmPC with a statement: Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found partially acceptable for the following reasons:

The applicant argued that the proposed Package Leaflet for Viramune prolonged-release tablets are based on the recently successfully tested and approved PL for Viramune 200 mg tablets and Viramune 50 mg/5 ml oral suspension (in May 2009) which contains nearly identical information and no significant changes are being made which would influence the readability.

The justification provided however cannot be endorsed due to the new dosing regimen of this new formulation and the safety differences between the approved and proposed package leaflets.

Therefore:

- the applicant will submit a bridging study based on the approved PL (resulting from the type II/82 variation) and to include the result of the testing into an upcoming application.

Combined Package Leaflet

The applicant proposes to have a separate package leaflet for the Viramune 400 mg prolonged-release tablet and a combined package leaflet for Viramune 100 mg and 50 mg based on the following:

- The posology in the SPC/PL mandates two dosages: a “lead-in” period of Viramune oral suspension once daily, after which the paediatric patient is switched to a maintenance dose of Viramune

prolonged-release 100 mg or 50 mg tablets once daily based on the body weight or body surface area.

- The Package Leaflets of the two different strengths are completely identical, except for few strength-specific details.
- The maintenance dose is calculated either according to body weight or body surface area. As a consequence the body weight and body height has to be checked frequently by the physician in order to adjust the dose if necessary. In the currently approved package leaflet for Viramune Oral Suspension no specific dose according to body weight or body surface area is given for the maintenance phase in order to avoid a wrong dosing by the child's parents. A general statement is given that the child's doctor will decide the right dose based either on the child's weight or body surface area. A similar wording is suggested for the paediatric strengths 100 mg and 50 mg of Viramune prolonged-release tablets. This guidance additionally avoids confusion of the patient.

The justifications for the request for a combined PL are found to be in line with the current QRD recommendations ("Compilation of QRD decisions on stylistic matters in product information") and therefore endorsed by CHMP.

2.8. Benefit-Risk Balance

Benefits

The beneficial effects obtained in the above presented clinical trials are consistent and in line with the body of knowledge previously described for the immediate release formulations.

Risks

- Unfavourable effects

The safety profile of the active pharmaceutical ingredient nevirapine has previously been established through the development and widespread use of nevirapine immediate release formulations. The drug substance used in the nevirapine prolonged-release formulation is identical to that used in nevirapine IR tablets. As expected, observed adverse events with nevirapine XR were expected to be very similar to those observed with nevirapine IR.

- Uncertainty in the knowledge about the unfavourable effects

Some expectation of a lower incidence of adverse events was hypothesized if a lower C_{max} could be achieved for the nevirapine XR formulation. Indeed, during the double-blind phase of study 1100.1486, a consistent trend was observed towards lower incidences in favour of nevirapine XR vs. nevirapine IR. This needs however to be confirmed in clinical practice (post-authorisation).

Benefit-risk balance

The prolonged-release formulation (XR) met the PK target levels, demonstrated non-inferior efficacy in comparison to nevirapine immediate release (IR) and exhibited similar safety. Therefore, the advantage of the once daily convenience of the prolonged-release formulation could be beneficial for patients.

3. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Viramune prolonged-release tablets indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adolescents and children three years and above and able to swallow tablets (not suitable for the 14-day lead-in phase for patients starting nevirapine) (50mg/100 mg) and indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents and children three years and above and able to swallow tablets (not suitable for the 14-day lead-in phase for patients starting nevirapine) (400 mg) was favourable and therefore recommended the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP. In this sense, it is agreed by CHMP to continue the currently pursued annual PSUR schedule, and to integrate nevirapine safety data for all dosage forms (immediate and prolonged-release tablets as well as oral suspension) into one document.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

None

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

None

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.