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RESEARCH**

APPLICATION NUMBER:
201152Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA: 201-152	Submission Date: June 3, 2010
Brand Name	VIRAMUNE® XR™
Generic Name	NEVIRAPINE
Reviewer	Vikram Arya, Ph.D.
Team Leader	Sarah M. Robertson, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Boehringer Ingelheim Pharmaceuticals Inc.
Relevant IND(s)	IND 74,744
Submission Type; Code	505 (b) (1), 1S
Formulation; Strength(s)	Tablet ; 400 mg
Dosing Regimen	<p>For patients initiating therapy with NEVIRAPINE® XR™ :</p> <p>One 200 mg tablet of immediate-release VIRAMUNE once daily for the first 14 days, followed by NEVIRAPINE® XR™ 400 mg once daily.</p> <p>For patients already on a regimen of immediate release VIRAMUNE 200 mg twice-daily:</p> <p>NEVIRAPINE® XR™ 400 mg once-daily (there is no need for lead in period with immediate release VIRAMUNE)</p>
Indication	Treatment of HIV-1 Infection

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1 Executive Summary

VIRAMUNE (nevirapine), a non-nucleoside reverse transcriptase inhibitor (NNRTI), is approved (with other antiretroviral agents; ARVs) for the treatment of HIV-1 infection in adult and pediatric patients. Nevirapine is currently approved as a 200 mg immediate release (IR) tablet and as an immediate release oral suspension (50 mg/5 mL).

Immediate release VIRAMUNE tablets received first marketing authorization in the United States in June 1996 (marketed as VIRAMUNE®). An oral suspension formulation was approved in 1998.

The approved regimens of immediate release VIRAMUNE in adult- and pediatric patients are shown in table 1.

Table 1: Approved Regimens of Immediate Release Nevirapine in Adult- and Pediatric Patients

	Adults (≥16 yrs)	Pediatric* (>15 days)
First 14 days	200 mg once daily	150 mg/m ² once daily
After 14 days	200 mg twice daily	150 mg/m ² twice daily

*Total daily dose should not exceed 400 mg for any patient.

The applicant has developed an extended-release (XR) 400 mg oral tablet formulation of nevirapine. The applicant is neither seeking a new indication nor proposing changes to the existing indication; the indications of the XR tablet are identical to the approved indication of the immediate release tablet.

The applicant conducted two Phase III trials in adult HIV-1 infected patients, **1100.1486** and **1100.1526**, to determine the safety and efficacy of the XR tablets.

Trial 1100.1486 was a randomized, double blind, non-inferiority trial to assess the safety and efficacy of NVP XR tablets (400 mg) administered once daily (+

Truvada) vs. NVP IR tablets (200 mg) twice daily (+Truvada) in treatment naïve, HIV-1 infected patients.

Trial 1100.1526 (also referred to as TRANxITION in the package insert) was a randomized parallel group trial to assess the efficacy and safety of switching HIV-1 infected patients successfully treated with a NVP IR 200 mg BID based regimen to a NVP XR 400 mg QD regimen vs. remaining on NVP IR 200 mg BID regimen.

The applicant also provided the results of 1100.1517, a single dose trial in adult subjects, which evaluated the bioavailability of 100 mg XR tablets, relative to 400 mg XR and 200 mg IR tablets. (b) (4)

1.1 Recommendation

The Clinical Pharmacology Information provided by the applicant is acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The applicant conducted two relative bioavailability trials, **1100.1485** (in healthy adult subjects) and **1100.1489** (in HIV-1 infected patients).

Trial 1100.1485 was an open-label, non-randomized, parallel group trial to evaluate the relative bioavailability of different oral VIRAMUNE XR formulations containing 300 mg or 400 mg NVP compared to 200 mg or 400 mg NVP as one or two 200 mg IR tablets following administration in healthy male volunteers.

Table 2 shows the evaluation of the relative bioavailability (nevirapine 400 mg IR formulation is the reference formulation) of the various extended release formulations evaluated in trial 1100.1485.

Table 2 : Evaluation of the relative bioavailability (nevirapine 400 mg IR formulation is the reference formulation) of the various extended release formulations evaluated in trial 1100.1485

Nevirapine	N	Inter-ind. gCV [%]	gMean Ratio (Test:Ref.) [%]	90% CI	
				Lower Limit [%]	Upper Limit [%]
AUC_{0-∞} dose normalised [ng·h/mL/mg]					
300 ECR20%	17	36.7	74.8	61.2	91.5
300 KCR20%	17	36.7	87.1	71.2	107.0
300 KCR25%	17	36.7	79.6	65.1	97.4
300 KCR30%	17	36.7	69.3	56.6	84.8
300 KCR40%	17	36.7	62.1	50.7	75.9
400 ECR20%	17	36.7	86.8	70.9	106.0
400 KCR20%	17	36.7	70.9	57.9	86.7
400 KCR25%	17	36.7	73.6	60.1	90.0
400 KCR30%	17	36.7	78.9	64.5	96.6
400 KCR40%	17	36.7	68.8	56.2	84.2
200 IR	17	36.7	109	88.9	133
C_{max} dose normalised [ng/mL/mg]					
300 ECR20%	17	30.3	71.0	60.0	84.0
300 KCR20%	17	30.3	70.8	59.8	83.7
300 KCR25%	17	30.3	75.5	63.8	89.3
300 KCR30%	17	30.3	57.3	48.4	67.8
300 KCR40%	17	30.3	57.8	48.8	68.3
400 ECR20%	17	30.3	63.8	53.9	75.5
400 KCR20%	17	30.3	63.8	53.9	75.5
400 KCR25%	17	30.3	63.0	53.2	74.5
400 KCR30%	17	30.3	67.7	57.2	80.0
400 KCR40%	17	30.3	51.4	43.5	60.8
200 IR	17	30.3	112	94.3	132
C₂₄ dose normalised [ng/mL/mg]					
300 ECR20%	17	34.0	88.7	73.5	106.9
300 KCR20%	17	34.0	87.9	72.9	106.0
300 KCR25%	17	34.0	92.8	77.0	111.9
300 KCR30%	17	34.0	67.6	56.0	81.5
300 KCR40%	17	34.0	67.9	56.3	81.9
400 ECR20%	17	34.0	77.8	64.5	93.8
400 KCR20%	17	34.0	80.3	66.6	96.8
400 KCR25%	17	34.0	74.8	62.0	90.2
400 KCR30%	17	34.0	75.6	62.7	91.2
400 KCR40%	17	34.0	62.6	51.9	75.5
200 IR	17	34.0	99.6	82.6	120.2

Source data: Table 15.5.3: 2

All the NVP XR formulations evaluated showed lower BA after single dose administration compared with NVP IR 400 mg (2 X 200 mg). Based on the results of the trial, two prototypes (KCR 25 % and KCR 20 %) at 300 mg and 400 mg were selected for further evaluation by the applicant.

Trial 1100.1489 was an open label, non-randomized, multiple-dose and multi-stage parallel group trial to evaluate the relative bioavailability (under fasted and fed conditions) of 2 different nevirapine XR formulations compared to 400 mg of immediate release NVP (200 mg BID) in HIV-1 infected patients.

Table 3 shows the computation of the relative bioavailability of NVP XR formulations administered under *fasted* conditions versus NVP IR 400 mg.

Table 3: Computation of the relative bioavailability of NVP XR formulations administered under *fasted* conditions versus NVP IR 400 mg

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC_{τ,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	79.5	73.0	86.7
400 mg KCR 20%	23/23	23.5	71.0	63.3	79.7
300 mg KCR 25%	20/20	22.1	90.3	80.4	101.4
300 mg KCR 20%	23/23	14.5	83.7	77.9	89.9
C_{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	70.2	64.6	76.3
400 mg KCR 20%	23/23	23.3	63.7	56.8	71.4
300 mg KCR 25%	20/20	22.6	77.0	68.3	86.7
300 mg KCR 20%	23/23	16.4	74.9	69.1	81.2
C_{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	89.6	80.6	99.6
400 mg KCR 20%	23/23	29.2	75.1	65.1	86.5
300 mg KCR 25%	20/20	32.0	99.4	84.2	117.4
300 mg KCR 20%	23/23	16.4	83.5	77.0	90.5

Source data: [Tables 15.5.1: 2, 15.5.1: 4, 15.5.1: 6, 15.5.1: 8, 15.5.1: 10, 15.5.1: 12, 15.5.1: 14, 15.5.1: 16, 15.5.1: 18, 15.5.1: 20, 15.5.1: 22, 15.5.1: 24](#)

Table 4 shows the computation of the relative bioavailability of NVP XR formulations administered under *fed* conditions versus NVP IR 400 mg.

Table 4 : Computation of the relative bioavailability of NVP XR formulations administered under *fed* conditions versus NVP IR 400 mg

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC_{τ,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	94.3	86.5	102.8
400 mg KCR 20%	23/23	23.5	89.7	80.0	100.6
300 mg KCR 25%	20/20	22.1	97.9	87.1	110.0
300 mg KCR 20%	23/23	14.5	101.7	94.7	109.3
C_{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	84.4	77.6	91.7
400 mg KCR 20%	23/23	23.3	85.2	76.1	95.5
300 mg KCR 25%	20/20	22.6	85.7	76.1	96.5
300 mg KCR 20%	22/23	16.4	96.8	89.2	105.1
C_{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	98.2	88.4	109.1
400 mg KCR 20%	23/23	29.2	86.6	75.1	99.8
300 mg KCR 25%	20/20	32.0	99.2	84.0	117.1
300 mg KCR 20%	23/23	16.4	96.5	89.0	104.6

Source data: [Tables 15.5.3: 1 to 15.5.3: 12](#)

(b) (4)

For additional details regarding trials 1100.1485 and 1100.1489, please refer to the individual trial reviews in the appendix.

2 Question based review (QBR)

2.1 General Attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).

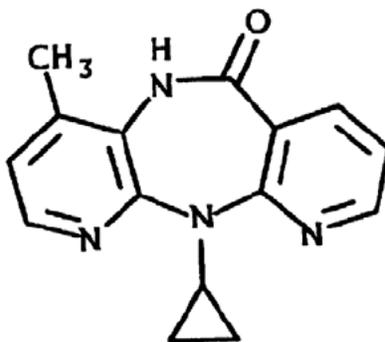


Table 5 shows the qualitative and quantitative composition of nevirapine extended release (XR) 400 mg tablets (final drug product).

Table 5: Qualitative and quantitative composition of nevirapine XR 400 mg tablets (final drug product)

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

(b) (4)

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependant and DNA-dependant polymerase activities by causing disruption of the enzyme's catalytic site.

Nevirapine, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection. The proposed indication for the XR tablet formulation is identical to the approved indication of the IR tablet.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed oral dose of NEVIRAPINE[®] XR[™] is 400 mg once daily. The XR tablet formulation can be taken with or without a meal.

The applicant has proposed the following dosing regimens:

For patients initiating therapy with NEVIRAPINE[®] XR[™]:

One 200 mg tablet of immediate-release VIRAMUNE once daily for the first 14 days, followed by NEVIRAPINE[®] XR[™] 400 mg once daily

For patients already on a regimen of immediate release VIRAMUNE 200 mg twice-daily:

NEVIRAPINE[®] XR[™] 400 mg once-daily (there is no need for lead in period with immediate release VIRAMUNE)

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant collected pivotal efficacy and safety data from two Phase III trials (1100.1486 and 1100.1526) in adult HIV-1 infected patients.

1100.1486

The major objective of trial 1100.1486 was to demonstrate non inferiority of the nevirapine XR tablets as compared with nevirapine IR tablets. All patients in the lead-in period received 200 mg QD of the IR formulation. After the lead-in period, the patients were randomized to receive either immediate release nevirapine 200 mg BID or nevirapine XR 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. The randomization

was stratified by screening HIV-1 RNA level ($\leq 100,000$ copies/mL and $> 100,000$ copies/mL). The duration of treatment was 48 weeks with an extension through 144 weeks.

The primary end point was sustained virologic response (viral load < 50 copies/mL) at week 48. Efficacy, safety, and pharmacokinetic data were evaluated at each study visit (visit 2 through visit 19; pre-treatment up to week 132). Table 6 shows the outcomes at week 48 in trial 1100.1486.

Table 6: Outcomes at Week 48 in Trial 1100.1486

	NVP 200 BID N=506	NVP XR 400 QD N=505
Virologic Success -HIV RNA ≤ 50 copies/mL	75%	80%
Virologic Failure#	13%	11%
No Virologic Data at 48 Window		
<u>Reasons</u>		
Discontinued trial/study drug due to AE or Death*	9%	7%
Discontinued trial/study drug for Other Reasons**	3%	2%
Missing data during window but on trial	<1%	

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

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

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

At week 48, mean change from baseline in CD4+ cell count adjusting for baseline HIV-1 viral load stratum was 191 cells/mm³ and 206 cells/mm³ for the groups receiving immediate-release VIRAMUNE and VIRAMUNE XR respectively.

Pharmacokinetic Assessments

For all patients, a pre-dose sample was collected at each visit within 1 hour of the planned dose. An optional PK sub-study included intensive PK sample collection on day 28 (week 4). Trough concentrations were determined by the pre-dose sample and additional PK parameters were determined based on concentrations determined in the optional PK study.

For the IR regimen, PK parameters are based on 25 patients with full concentration time profile and mean trough concentrations are based on 372 patients. For the XR regimen, the PK parameters are based on 24 patients with full concentration time profile and the mean trough concentrations are based on 406 patients.

Table 7 shows the mean PK parameters (based on intensive sampling and sparse PK sampling) in the trial.

Table 7: Mean PK parameters (based on intensive sampling and sparse PK sampling) in the trial

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

gMean: geometric mean
Source data: [Tables 15.6.2.1: 1-2](#)

Table 8 shows the mean trough concentrations of nevirapine after administration of NVP XR 400 mg QD and NVP IR 200 mg BID.

Table 8: Mean trough concentrations of nevirapine after administration of NVP XR 400 mg QD and NVP IR 200 mg BID

	Week	4	6	8	12	16	24	32	40	48
NVP IR 200 mg BID	N	358	352	346	338	345	345	335	321	321
	Mean	4,630	4,450	4,380	4,330	4,420	4,550	4,550	4,680	4,910
	CV (%)	49	49.3	49.6	47	51.5	54.1	49.2	50.7	49.2
	gMean	4,220	4,070	3,950	3,950	3,980	4,120	4,120	4,250	4,460
	P10	2,670	2,600	2,510	2,510	2,500	2,620	2,640	2,650	2,820
NVP XR 400 mg QD	N	418	407	420	423	417	393	385	382	376
	Mean	3,880	3,580	3,490	3,540	3,560	3,540	3,780	3,870	3,840
	CV (%)	45.7	43.6	45.2	43.7	47.5	43.5	44.8	44.2	45.4
	gMean	3,500	3,260	3,150	3,190	3,190	3,180	3,420	3,520	3,430
	P10	2,030	1,880	1,840	1,860	1,850	1,910	2,010	2,060	1,920
XR/IR gMean (%)		82.9	80.1	79.7	80.8	80.2	77.2	83.0	82.8	76.9

P10: 10th percentile
Source data: [Tables 15.6.2.1: 11-12](#)

Fig 1 shows the box plot of the plasma nevirapine trough concentrations at Week 48 after administration of NVP XR 400 mg QD and NVP IR 200 mg BID.

Fig 1: Box plot of the plasma nevirapine trough concentrations at Week 48 after administration of NVP XR 400 mg QD and NVP IR 200 mg BID

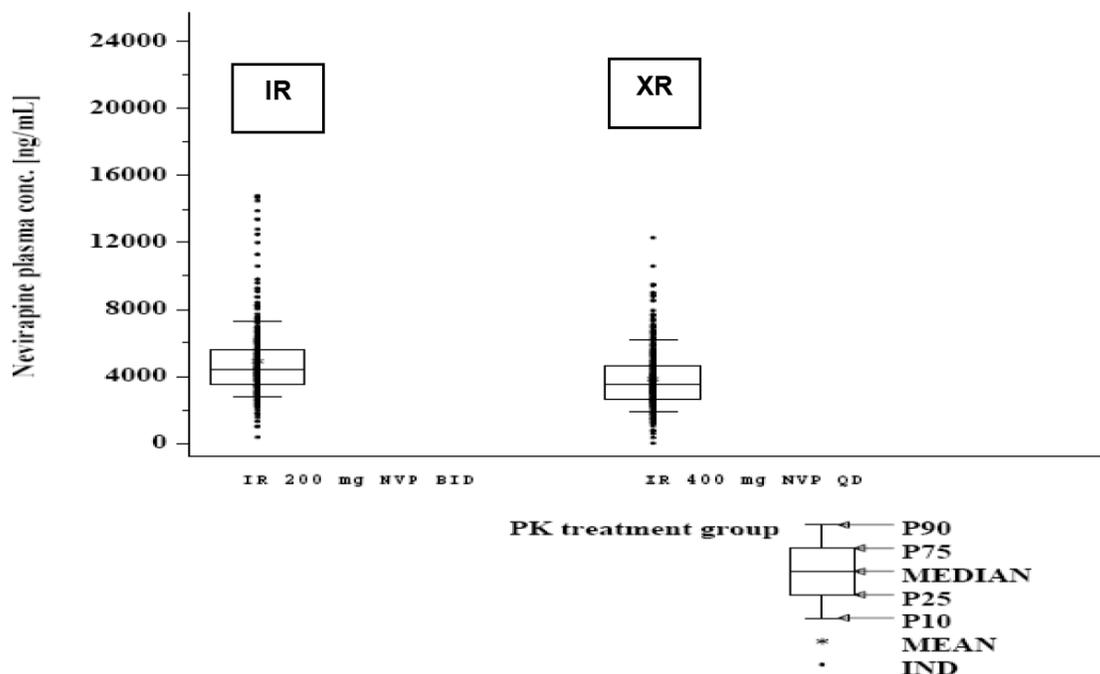


Table 9 shows the relative bioavailability and geometric means of pharmacokinetic sub-study parameters and trough concentrations of nevirapine.

Table 9: Relative bioavailability and geometric means of pharmacokinetic sub-study parameters and trough concentrations of nevirapine

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_{0-24,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

Source data: [Tables 15.5.1: 1-2](#)

1100.1526 (TRANxITION trial)

The major objective of this ongoing (24-week data provided in the submission), randomized, open label trial was to evaluate the safety and antiviral activity of switching from immediate-release VIRAMUNE to VIRAMUNE XR. In this open-label trial, 443 patients already on an antiviral regimen containing immediate-release VIRAMUNE 200 mg twice daily with HIV-1 RNA < 50 copies/mL were randomized in a 2:1 ratio to VIRAMUNE XR 400 mg once daily or immediate-release VIRAMUNE 200 mg twice daily. Approximately half of the patients had tenofovir+emtricitabine as their background therapy, while the remaining patients receiving abacavir sulfate+lamivudine or zidovudine+lamivudine. Approximately half of the patients had at least 3 years of prior exposure to immediate-release VIRAMUNE prior to entering Trial 1100.1526.

At 24 weeks after randomization in the trial, 94 % and 95 % of patients receiving immediate-release VIRAMUNE 200 mg twice daily or VIRAMUNE XR 400 mg once daily, respectively, continued to have HIV-1 RNA < 50 copies/mL.

Pharmacokinetic Assessments

The applicant only collected trough samples during visit 2 to visit 9.

Table 10 shows the comparison of the trough concentrations of nevirapine after administration of VIRAMUNE 400 mg QD XR formulation and 200 mg BID IR formulation.

Table 10: Comparison of the trough concentrations of nevirapine after administration of VIRAMUNE 400 mg QD XR formulation and 200 mg BID IR formulation

Treatment		Trough Concentration (ng/mL) at Week					
		0	2	4	8	12	24
XR Tablet 400 mg QD	Mean	-- ^a	3740	3580	4060	3980	4040
	%CV	--	58.7	52.9	52.6	51.7	42.7
	gMean	--	3270	3220	3680	3590	3730
	P10	--	1840	1840	2260	2080	2290
	N	--	225	231	221	217	207
IR Tablet 200 mg BID	Mean	4210	3980	4040	4360	4470	4340
	%CV	46.2	38.5	38.1	38.3	39.1	37.8
	gMean	3730	3710	3770	4080	4160	4070
	P10	2130	2240	2310	2630	2550	2510
	N	145	110	110	113	110	110

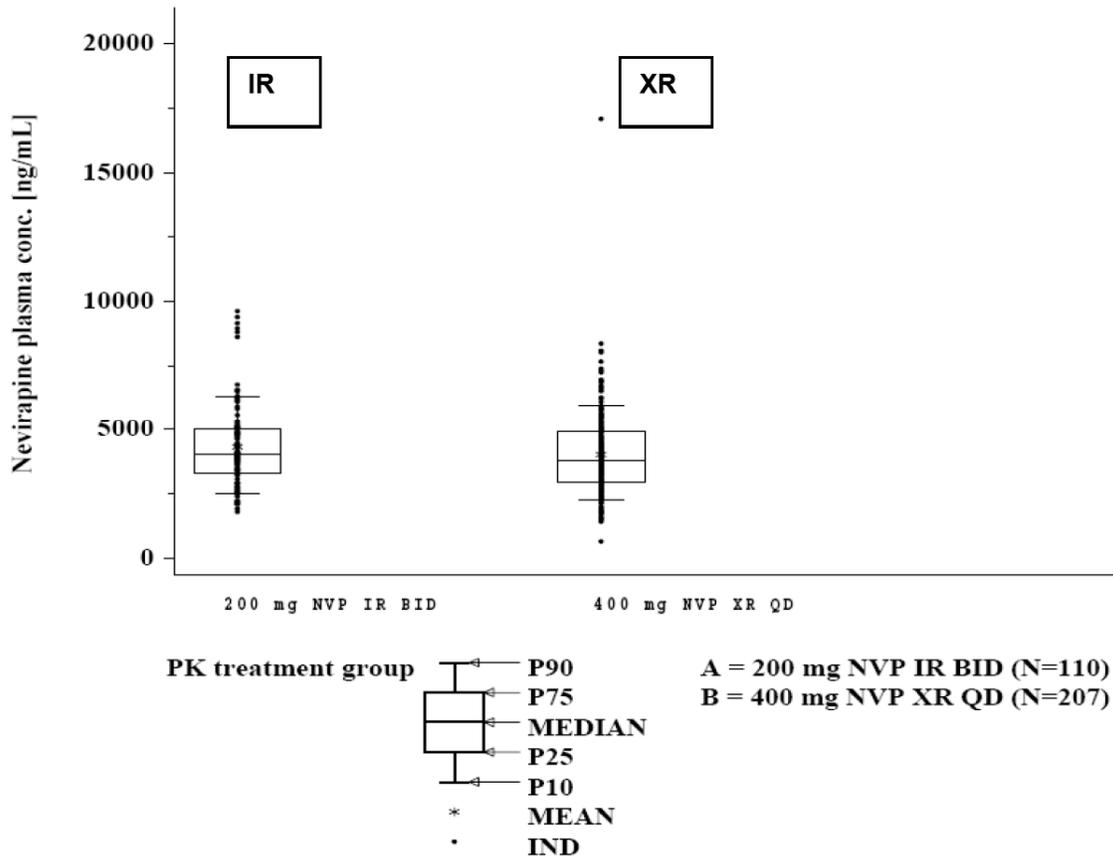
a: Prior to randomization

P10: 10th percentile.

Source data: [Section 15.6.3](#)

Fig 2 shows the box plot of the plasma nevirapine trough concentrations at Week 24 after administration of NVP XR 400 mg QD and NVP IR 200 mg BID.

Fig 2: Box plot of the plasma nevirapine trough concentrations at Week 24 after administration of NVP XR 400 mg QD and NVP IR 200 mg BID



2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or Surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4+ cell count are accepted as surrogate markers for efficacy in trials with antiretroviral (ARV) agents. In trials 1100.1486 and 1100.1526 (ongoing trial), the primary end point was sustained virologic response (< 50 copies/mL) at Week 48 and Week 24, respectively. In addition, effects on CD4+ cell count were also assessed.

2.2.3. Are the active moieties in the plasma (or other biological fluid) Appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, the applicant quantified nevirapine in plasma using validated HPLC/MS/MS methods.

2.2.4 Exposure-Response

- 2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Based on the applicant's analysis, the XR formulation of nevirapine was expected to show an average (\pm s.d.) nevirapine concentration of 3000 (\pm 500 ng/mL) ng/mL. The applicant previously conducted a population pharmacokinetic analysis of pharmacokinetic data generated using the nevirapine immediate release formulation (2NN trial). The results of the analysis suggested that maintaining a nevirapine trough concentration above 1000 ng/mL is not expected to result in a loss of efficacy. Of note, in trial 1100.1486, the geometric mean C_{minss} observed at week 48 after administration of 400 mg XR QD and 200 mg IR BID was 3430 ng/mL and 4460 ng/mL, respectively. In trial 1100.1526, the the geometric mean C_{minss} observed at week 24 after administration of 400 mg XR QD and 200 mg IR BID was 3730 ng/mL and 4070 ng/mL, respectively.

2.2.5. What are the PK characteristics of Nevirapine XR?

- 2.2.5.1. What are the single dose and multiple dose PK parameters?

The applicant determined the single-dose pharmacokinetics of nevirapine in trial 1100.1485 in which the bioavailability of nevirapine (administered as different oral VIRAMUNE extended release formulations) was determined relative to nevirapine immediate release formulation in healthy volunteers.

Table 11 shows the mean systemic exposure of nevirapine after single dose administration of various XR formulations and the 200 mg IR formulation.

Table 11: Mean systemic exposure of nevirapine after single dose administration of various XR formulations and the 200 mg IR formulation

Nevirapine	N	AUC ₀₋		AUC _{0-tz}		C _{max}		C ₂₄		C _{max} /C ₂₄	
		gMean [ng·h/mL]	gCV [%]	gMean [ng·h/mL]	gCV [%]	gMean [ng/mL]	gCV [%]	gMean [ng/mL]	gCV [%]	gMean	gCV [%]
300 ECR20%	17	118000	30.4	108000	27.6	1660	26.1	1640	26.5	1.01	3.87
300 KCR20%	17	137000	50.4	117000	47.8	1660	42.3	1630	46.1	1.02	5.08
300 KCR25%	17	126000	33.7	114000	30.4	1770	25.3	1720	30.1	1.03	6.36
300 KCR30%	17	109000	28.6	94800	28.1	1340	27.4	1250	33.4	1.07	13.2
300 KCR40%	17	97800	63.6	87500	59.9	1350	43.9	1260	57.1	1.08	14.2
400 ECR20%	17	182000	31.2	156000	26.1	1990	28.1	1920	29.0	1.04	6.27
400 KCR20%	17	149000	31.6	135000	29.4	1990	26.7	1980	27.3	1.01	2.44
400 KCR25%	17	155000	29.4	137000	30.5	1970	32.2	1840	37.0	1.07	13.8
400 KCR30%	17	166000	27.9	149000	25.5	2110	20.9	1870	27.5	1.13	15.2
400 KCR40%	17	145000	46.7	123000	46.6	1610	43.0	1540	44.7	1.04	5.22
200 IR	17	114000	29.6	98800	21.8	1740	20.8	1230	16.7	1.42	18.6
400 IR	17	210000	22.3	187000	17.0	3130	11.7	2470	10.5	1.27	11.9

Source data: Table 15.5.2.1: 1-12

The applicant determined the multiple-dose pharmacokinetics of nevirapine in trial 1100.1489 in which the bioavailability of nevirapine (administered as different oral VIRAMUNE XR formulations) was determined relative to nevirapine IR formulation in HIV-1 infected patients.

Table 12 shows the mean systemic exposure of nevirapine after multiple-dose administration of various XR formulations and the 200 mg IR formulation in HIV-1 infected patients.

Table 12: Mean systemic exposure of nevirapine after multiple dose administration of various XR formulations and the 200 mg IR formulation in HIV-1 infected patients

Parameter	Units		Treatment A			Treatment B		
			NVP XR 400 mg KCR 25%			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	5950	4140	5010	7340	4850	6230
		(%CV)	(26.8)	(22.4)	(25.6)	(33.9)	(42.3)	(31.8)
		gMean	5750	4040	4850	7000	4470	5980
$C_{min,ss}$	[ng/mL]	mean	3240	2920	3150	4500	3600	4010
		(%CV)	(30.9)	(32.3)	(27.7)	(40.0)	(49.0)	(43.8)
		gMean	3090	2770	3030	4220	3190	3680
$\frac{C_{max,ss}}{C_{min,ss}}$		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	4280	3420	4030	5690	4220	5140
		(%CV)	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	4140	3290	3900	5390	3860	4880
$AUC_{\tau,ss}$	[ng·h/mL]	mean	103000	82000	96700	137000	101000	123000
		(%CV)	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	99400	79000	93700	129000	92700	117000
$\frac{AUC_{\tau,ss,5'}}{AUC_{\tau,ss,6}}$		mean	1.08	---	---	1.02	---	---
		(%CV)	(11.8)	---	---	(8.69)	---	---
		gMean	1.08	---	---	1.02	---	---
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

Source data: [Table 15.6.2.1.1 to Table 15.6.2.1.6](#)

(b) (4)

2.3 General Biopharmaceutics

2.3.1: What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The applicant used the final drug product in the pivotal clinical trials; therefore, a relative bioavailability trial was not needed.

2.3.2 What data support or do not support a waiver of *in vivo* BE data?

The applicant intends to market only the 400 mg XR tablet; therefore, there was no biowaiver request.

2.3.3 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90 % CI using equivalence limits of 80-125 %.

The results of trial 1100.1485 showed that the mean relative bioavailability of NVP, when nevirapine was administered as a single dose of various XR formulations, relative to the IR formulation was approximately 75 % {60 %-90 %}. This comparison was based on the AUC of the 400 mg 25 % KCR formulation (b) (4) and a single 400 mg dose using the 200 mg IR tablets. Although the BA of the XR formulation, relative to the IR formulation, was outside the the traditional 80-125 % limits, this is not clinically relevant because:

- 1) Trial 1100.1485 was designed as a parallel group vs a crossover trial (traditionally used in bioequivalence trials) because the trial was primarily designed to select an extended release formulation for subsequent development. Hence, differences in variability between the IR and XR group can result in biased estimates of bioavailability.
- 2) The mean (90 % CI) relative bioavailability of VIRAMUNE XR vs. nevirapine IR in HIV-1 infected patients (assessed in a crossover manner in trial 1100.1489), when nevirapine was given under fasted and fed conditions was 80 % (73 %-86.7 %) and 94 % (86.5 %- 102.8 %), respectively, thereby suggesting that the systemic exposures of nevirapine after the administration of VIRAMUNE XR and IR formulations were similar in the population of interest (HIV-1 infected patients).
- 3) The efficacy results from pivotal trials 1100.1486 and 1100.1526 showed that the efficacy of nevirapine was similar after administration of nevirapine IR (200 mg BID) and nevirapine XR (400 mg QD) at Week 48 (trial 1100.1486) and Week 24 (trial 1100.1526), respectively.

2.3.4 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

See point # 3 in response to question 2.3.3.

2.3.5 What is the effect of food on the bioavailability (BA) of NVP XR
What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Trial 1100.1489 assessed the effect of food on the the rate and extent of absorption of the NVP XR formulation by comparing the steady state exposure of the NVP XR formulation administered after a meal (high-fat) compared with the NVP XR formulation given under fasted conditions.

Table 13 shows the computation of the relative bioavailability of NVP XR formulations administered under fasted vs fed conditions at steady state.

Table 13: Computation of the relative bioavailability of NVP XR formulations administered under fasted vs fed conditions at steady-state

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC_{r,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	118.5	108.8	129.2
400 mg KCR 20%	23/23	23.5	126.3	112.6	141.7
300 mg KCR 25%	20/20	22.1	108.4	96.5	121.8
300 mg KCR 20%	23/23	14.5	121.6	113.2	130.6
C_{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	120.2	110.6	130.7
400 mg KCR 20%	23/23	23.3	133.8	119.4	150.0
300 mg KCR 25%	20/20	22.6	111.4	98.9	125.4
300 mg KCR 20%	22/23	16.4	129.3	119.1	140.3
C_{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	109.6	98.6	121.8
400 mg KCR 20%	23/23	29.2	115.3	100.0	132.9
300 mg KCR 25%	20/20	32.0	99.8	84.5	117.8
300 mg KCR 20%	23/23	16.4	115.5	106.6	125.3

Source data: [Tables 15.5.2: 1 to 15.5.2: 12](#)

The difference in the bioavailability of nevirapine, when VIRAMUNE XR is dosed under fasted or fed conditions, is not considered clinically relevant. Therefore, VIRAMUNE XR can be taken with or without food.

2.3.6 When would a fed BE study be appropriate and was one conducted?

Not applicable to this NDA.

2.3.7 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the review from the Office of New Drug Quality Assessment (ONDQA).

2.3.8 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable to this NDA.

- 2.3.9 If the NDA is for a modified release formulation of an unapproved immediate product without supportive safety and efficacy studies, what dosing regimen change are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable to this NDA because the immediate release formulation of nevirapine is approved.

- 2.3.10 What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?

There are no other BA and BE issues that need to be further addressed. For information pertaining to *in vitro* dissolution, please refer to the review from ONDQA.

2.4. Analytical Section

- 2.4.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moiety was identified and measured in the plasma by using validated LC/MS/MS methods.

- 2.4.2. Which metabolites have been selected for analysis and why?

The sponsor did not measure any metabolites of nevirapine.

- 2.4.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods used measured the total concentrations of nevirapine. Although measurement of free concentrations may be more clinically relevant, it is standard to measure total concentrations of non-nucleoside reverse transcriptase inhibitors.

- 2.4.4 What bioanalytical methods are used to assess concentrations?

Please refer to the individual trial reviews for the details of the analytical methodology.

3 Labeling Recommendations

The following section of the label (section 12.3) reflects the final labeling language and incorporates the suggestions provided to the applicant by the clinical pharmacology review team during the review process.

12.3 Pharmacokinetics

Adults

Absorption and Bioavailability

The single-dose pharmacokinetics of VIRAMUNE XR was studied in 17 healthy volunteers. Nevirapine was absorbed with a median t_{\max} of approximately 24 hrs. The mean C_{\max} and $AUC_{0-\infty}$ of nevirapine were 2060 ng/mL and 161000 ng*hr/mL, respectively. The bioavailability of 400 mg NVP XR, relative to 400 mg VIRAMUNE IR, was approximately 75%.

The multiple-dose pharmacokinetics of VIRAMUNE XR was studied in 24 HIV-1 infected patients who switched from chronic VIRAMUNE IR to VIRAMUNE XR. The mean nevirapine $AUC_{0-24,ss}$ and $C_{\min,ss}$ after 19 days of VIRAMUNE XR dosing under fasted conditions were 82000 ng*hr/mL and 2920 ng/mL, respectively. When VIRAMUNE XR was administered under fed conditions, the mean nevirapine $AUC_{0-24,ss}$ and $C_{\min,ss}$ were 96700 ng*hr/mL and 3150 ng/mL, respectively. The bioavailability of 400 mg NVP XR, relative to 400 mg VIRAMUNE IR, under fasted and fed conditions, was 80 % and 94 %, respectively. The difference in the bioavailability of nevirapine, when VIRAMUNE XR is dosed under fasted or fed conditions, is not considered clinically relevant. VIRAMUNE XR can be taken with or without food.

The other clinical pharmacology information in the nevirapine XR label is similar to the clinical pharmacology information in the approved nevirapine IR label.

4 Appendices

4.1 Individual Trial Reviews

Study Number

1100.1485

Title

Relative bioavailability of different oral Viramune[®] extended release formulations containing 300 mg or 400 mg NVP compared to 200 mg or 400 mg NVP as one or two 200 mg IR tablets following administration in healthy male volunteers-an open-label, non-randomized, parallel group study.

Objectives

The primary objective of the current study was to investigate the relative bioavailability of various extended release formulations (test, T) containing 300 mg or 400 mg nevirapine compared to 200 mg or 400 mg nevirapine as one or two 200 mg immediate release tablets.

Study Design

Open label, randomized, parallel group design. 17 subjects were planned to be evaluated per treatment group.

Following an overnight fast of at least 10 hours, single dose of nevirapine was administered with approximately 240 mL of water. The subjects were monitored for 2 hours after drug administration. Water was allowed *ad libitum* except for one hour before and one hour after drug administration. The standardized meals were served at 4 hours, 10 hours, and 14 hours following drug administration.

Table 1 shows the various formulations that were evaluated in the trial.

Table 1: Various formulations evaluated in the trial

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%

(b) (4)

Pharmacokinetic Sampling Schedule and Determination of Plasma Concentration of NVP

Sampling Schedule

The plasma samples for the determination of nevirapine concentrations were collected at the following time points:

Day 1: pre-dose (1 hour before drug administration) and 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 16 hours after dosing.

Day 2 through day 7: 24, 36, 48, 72, 96, and 144 hours after dosing on day 1.

Determination of Plasma Concentration of NVP

The plasma concentration of NVP was determined by a validated HPLC-MS/MS method. The details of the assay methodology are presented in table 2 below.

Table 2: Details of assay methodology

Analyte		Nevirapine	
Internal Standard		(b) (4)	
Matrix / Anticoagulant		K ₃ EDTA	
Assay Volume Required		50.0 µL	
Extraction		Protein precipitation	
Detection Method		HPLC with MS/MS	
Standard Curve Range		25.0 to 10,000 ng/mL	
Regression Type		Quadratic, 1/concentration squared	
Parameters	Acceptance Criteria ^a	Intra-run ^b	Inter-run ^b
Accuracy of QCs, %RE (LLOQ)	± 15 (± 20)	10.2	4.46
Precision of QCs, %RSD (LLOQ)	≥ 15 (≤ 20)	7.67 ^c	11.7
r ² of Calibration Curves	≥ 0.9900	0.9979	
% RE of Calibration Curves (LLOQ)	± 15 (± 20)	3.55	
% RSD of Calibration Curves (LLOQ)	≤ 15 (≤ 20)	6.74	
Dilution QC (10-Fold)	± 15	4.57	
Stability in Plasma Freeze-Thaw	± 15	4 cycles at room temperature	
Stability in Plasma Room Temperature	± 15	24 hours at room temperature	
Stability of Processed Sample Extract	± 15	23 hours at room temperature	
Stability in Plasma Freezer Storage	± 15 ^d	268 days at -20° C	
Stability of Stock Solution in methanol stored at 2 to 8 °C	± 5 ^e ± 20 ^e	Nevirapine: 1.00 mg/mL solution for 664 days (b) (4) 0.100 mg/mL solution for 53 days	

^a Reference: (b) (4) SOP LP-BA-003 unless otherwise noted

^b Results listed are absolute values

^c Excluding (b) (4) value at the LLOQ

^d Reference: (b) (4) SOP LP-BA-017

^e Reference: (b) (4) SOP LP-BA-016

Pharmacokinetic Analysis

The descriptive analysis of the NVP concentration values, calculation of the pharmacokinetic parameters, and the descriptive analysis of the pharmacokinetic parameters were performed using Winnonlin[®]. In the non-compartmental analysis, the concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable), were ignored and not replaced with zero. The descriptive statistics of concentrations at specific time points were calculated only when at least 2/3 of the individuals had concentrations within the validated concentration range. The overall sample size to determine the whether the “2/3 rule” was fulfilled was based on the total number of samples intended to be drawn for that time point, i.e., BLQ, NOR, NOS, NOA, and NOP were included.

In the non-compartmental analysis, the concentration data identified with NOR, NOS, NOA was not considered. The BLQ and NOP values were set to zero. If the pre-dose concentration was less than or equal to 5 % of the C_{max} value in that subject, the subject’s data without any adjustments could be included in all pharmacokinetic assessments and calculations. If the pre-dose concentration was > 5 % of the C_{max} , the subject was dropped from all statistical evaluations.

RESULTS

Subject Disposition and Demographics

All 204 subjects who were enrolled completed the trial (n = 17 per test treatment and reference treatment). There were no premature discontinuations in the trial

Table 3 shows the demographics of the subjects enrolled in the trial.

Table 3: Demographics of the subjects enrolled in the trial

	ER300med20	ER300med25	ER300slow30	ER400med25	ER300slow40	ER300fast	ER400med20
Number of subjects	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)
Sex							
Male	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)
Female	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Age [years]							
N	17	17	17	17	17	17	17
Mean	34.1	33.8	36.3	34.8	37.8	33.1	33.6
SD	9.9	7.0	8.0	9.6	8.7	7.7	8.7
Min	19	23	20	21	22	20	19
Median	33.0	34.0	39.0	34.0	38.0	31.0	33.0
Max	50	46	47	50	49	50	46
Race							
White	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)
Black	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Asian	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Smoking status							
Never smoked	8(47.1)	3(17.6)	6(35.3)	3(17.6)	6(35.3)	4(23.5)	7(41.2)
Ex smoker	3(17.6)	3(17.6)	5(29.4)	3(17.6)	2(11.8)	5(29.4)	4(23.5)
Smoker	6(35.3)	11(64.7)	6(35.3)	11(64.7)	9(52.9)	8(47.1)	6(35.3)
Alcohol status							
Non drinker	8(47.1)	10(58.8)	6(35.3)	9(52.9)	8(47.1)	9(52.9)	7(41.2)
Drinks - no interf.	9(52.9)	7(41.2)	11(64.7)	8(47.1)	9(52.9)	8(47.1)	10(58.8)
Drinks - poss.interf	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

	ER400slow30	ER400slow40	ER400fast	IR400comm	IR200comm	Total
Number of subjects	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	204(100.0)
Sex						
Male	17(100.0)	17(100.0)	17(100.0)	17(100.0)	17(100.0)	204(100.0)
Female	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Age [years]						
N	17	17	17	17	17	204
Mean	33.4	35.2	32.3	31.9	33.0	34.1
SD	9.6	9.3	6.8	9.3	9.1	8.6
Min	21	20	22	20	19	19
Median	31.0	36.0	32.0	28.0	35.0	34.0
Max	50	46	44	46	49	50
Race						
White	17(100.0)	17(100.0)	16(94.1)	17(100.0)	17(100.0)	203(99.5)
Black	0(0.0)	0(0.0)	1(5.9)	0(0.0)	0(0.0)	1(0.5)
Asian	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Smoking status						
Never smoked	7(41.2)	6(35.3)	8(47.1)	4(23.5)	7(41.2)	69(33.8)
Ex smoker	3(17.6)	2(11.8)	4(23.5)	3(17.6)	5(29.4)	42(20.6)
Smoker	7(41.2)	9(52.9)	5(29.4)	10(58.8)	5(29.4)	93(45.6)
Alcohol status						
Non drinker	5(29.4)	10(58.8)	10(58.8)	9(52.9)	9(52.9)	100(49.0)
Drinks - no interf.	12(70.6)	7(41.2)	7(41.2)	8(47.1)	8(47.1)	104(51.0)
Drinks - poss.interf	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

PHARMACOKINETICS

Fig 1 shows the geometric mean of the nevirapine plasma concentrations as a function of time after oral administration of 300 mg (A) and 400 mg (B) of various extended release formulations compared with nevirapine 400 mg IR formulation (lower panel)

Fig 1: Geometric mean of the nevirapine plasma concentrations as a function of time after oral administration of 300 mg (A) and 400 mg (B) of various extended release formulations compared with nevirapine 400 mg IR formulation (lower panel)

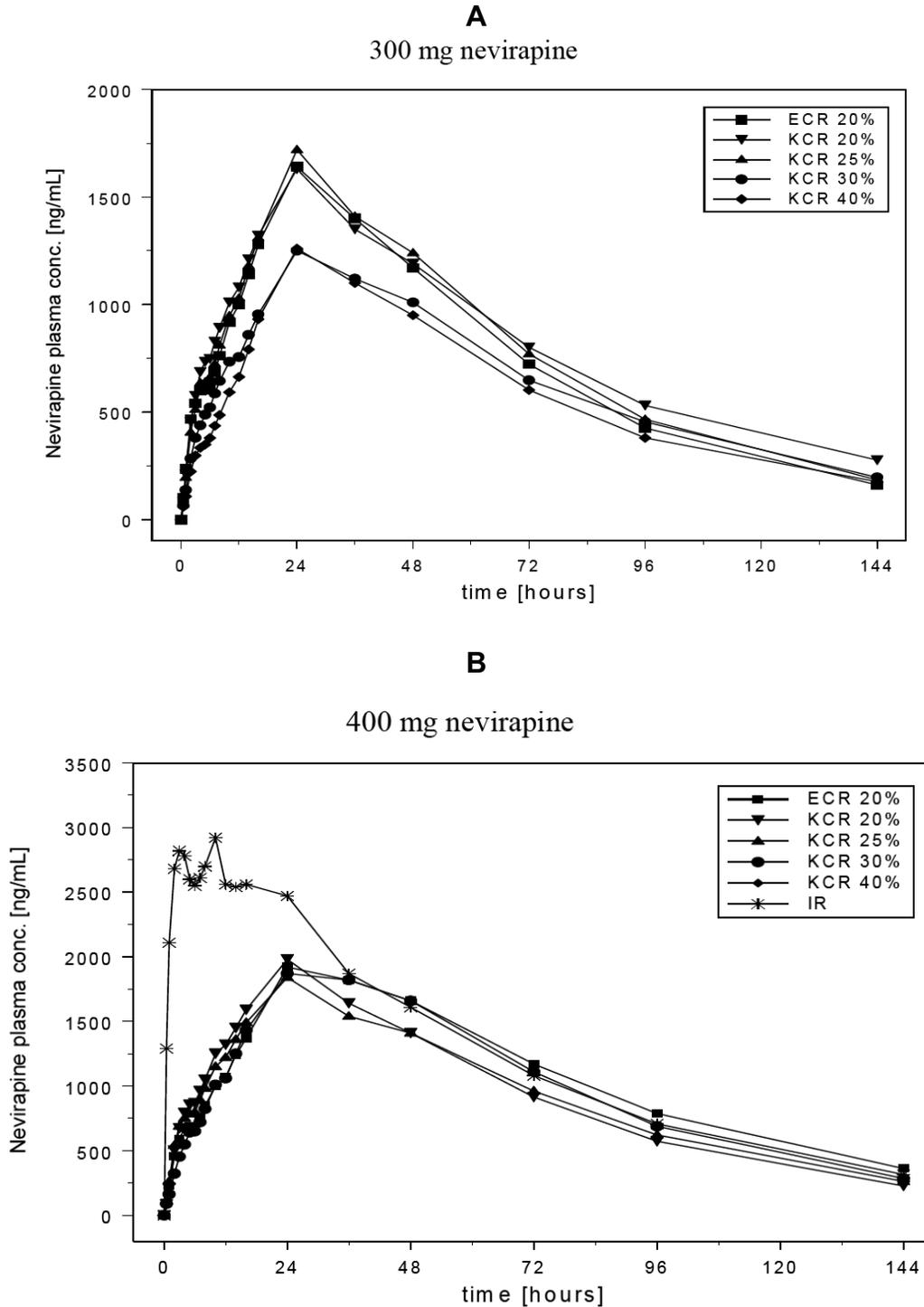


Table 4 shows the geometric mean (geometric % CV) pharmacokinetic parameters of nevirapine ER and nevirapine IR

Table 4: Geometric mean (geometric % CV) pharmacokinetic parameters of nevirapine ER and nevirapine IR

Nevirapine	N	AUC ₀₋		AUC _{0-tz}		C _{max}		C ₂₄		C _{max} /C ₂₄	
		gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV
		[ng·h/mL]	[%]	[ng·h/mL]	[%]	[ng/mL]	[%]	[ng/mL]	[%]		[%]
300 ECR20%	17	118000	30.4	108000	27.6	1660	26.1	1640	26.5	1.01	3.87
300 KCR20%	17	137000	50.4	117000	47.8	1660	42.3	1630	46.1	1.02	5.08
300 KCR25%	17	126000	33.7	114000	30.4	1770	25.3	1720	30.1	1.03	6.36
300 KCR30%	17	109000	28.6	94800	28.1	1340	27.4	1250	33.4	1.07	13.2
300 KCR40%	17	97800	63.6	87500	59.9	1350	43.9	1260	57.1	1.08	14.2
400 ECR20%	17	182000	31.2	156000	26.1	1990	28.1	1920	29.0	1.04	6.27
400 KCR20%	17	149000	31.6	135000	29.4	1990	26.7	1980	27.3	1.01	2.44
400 KCR25%	17	155000	29.4	137000	30.5	1970	32.2	1840	37.0	1.07	13.8
400 KCR30%	17	166000	27.9	149000	25.5	2110	20.9	1870	27.5	1.13	15.2
400 KCR40%	17	145000	46.7	123000	46.6	1610	43.0	1540	44.7	1.04	5.22
200 IR	17	114000	29.6	98800	21.8	1740	20.8	1230	16.7	1.42	18.6
400 IR	17	210000	22.3	187000	17.0	3130	11.7	2470	10.5	1.27	11.9

Source data: Table 15.5.2.1: 1-12

Nevirapine	N	t _{max}		k _a		t _{1/2}		MRT _{po}		CL/F		V _z /F	
		Median	Range	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV	gMean	gCV
		[h]	[h]	[1/h]	[%]	[h]	[%]	[h]	[%]	[mL/min]	[%]	[L]	[%]
300 ECR20%	17	24.0	16.1 36.0	0.0491	48.5	33.9	27.8	62.6	20.7	42.4	30.4	124	31.5
300 KCR20%	17	24.0	10.0 36.0	0.0711	45.9	43.6	35.4	74.4	31.1	36.4	50.4	137	43.7
300 KCR25%	17	24.0	10.0 36.0	0.052	75.1	36.1	25.8	65.0	18.9	39.8	33.7	124	29.2
300 KCR30%	17	24.0	10.0 48.2	0.0564	78.2	42.8	28.1	74.8	22.7	45.8	28.6	170	36.8
300 KCR40%	17	24.1	7.0 48.5	0.0456	85.6	36.5	30.2	67.1	27.7	51.1	63.6	161	48.3
400 ECR20%	17	24.1	24.0 48.1	0.0437	42.9	44.1	28.4	79.4	23.1	36.5	31.2	139	27.7
400 KCR20%	17	24.0	16.0 36.0	0.0646	46.8	36.9	21.4	65.6	16.4	44.8	31.6	143	27.3
400 KCR25%	17	24.0	10.0 48.0	0.0608	76.1	40.0	26.3	71.0	22.0	43.1	29.4	149	44.0
400 KCR30%	17	24.2	10.0 47.9	0.0384	61.9	37.6	20.5	70.3	18.1	40.2	27.9	131	27.9
400 KCR40%	17	24.0	10.0 48.1	0.0416	76.9	45.1	21.2	80.6	17.0	46.1	46.7	180	53.3
200 IR	17	2.0	0.5 24.4	n.d.	n.d.	47.4	25.4	70.3	23.6	29.2	29.6	120	13.0
400 IR	17	3.0	1.0 24.0	n.d.	n.d.	42.7	27.2	64.1	25.4	31.7	22.3	117	13.4

n.d. = not determined

range = minimum; maximum

Source data: Table 15.5.2.1: 1-12

The AUC_{0-∞} after single dose treatment with nevirapine ER formulations ranged between 97800 ng·h/mL and 137000 ng·h/mL for the 300 mg dose and between 145000 ng·h/mL and 182000 ng·h/mL for the 400 mg dose. For the 400 mg nevirapine ER formulations, AUC_{0-∞} was about 69 % to 87 % of the AUC_{0-∞} observed for 400 mg nevirapine IR. The geometric mean of the extrapolated

fraction of $AUC_{0-\infty}$ (% $AUC_{tz-\infty}$) ranged between 6.6 % and 13.6 % for all treatments.

Fig 2 shows the distribution of the individual C_{max} and $AUC_{0-\infty}$ of nevirapine by dose (300 mg) and various extended release formulations

Fig 2: Distribution of the individual C_{max} and $AUC_{0-\infty}$ of nevirapine by dose (300 mg) and various extended release formulations

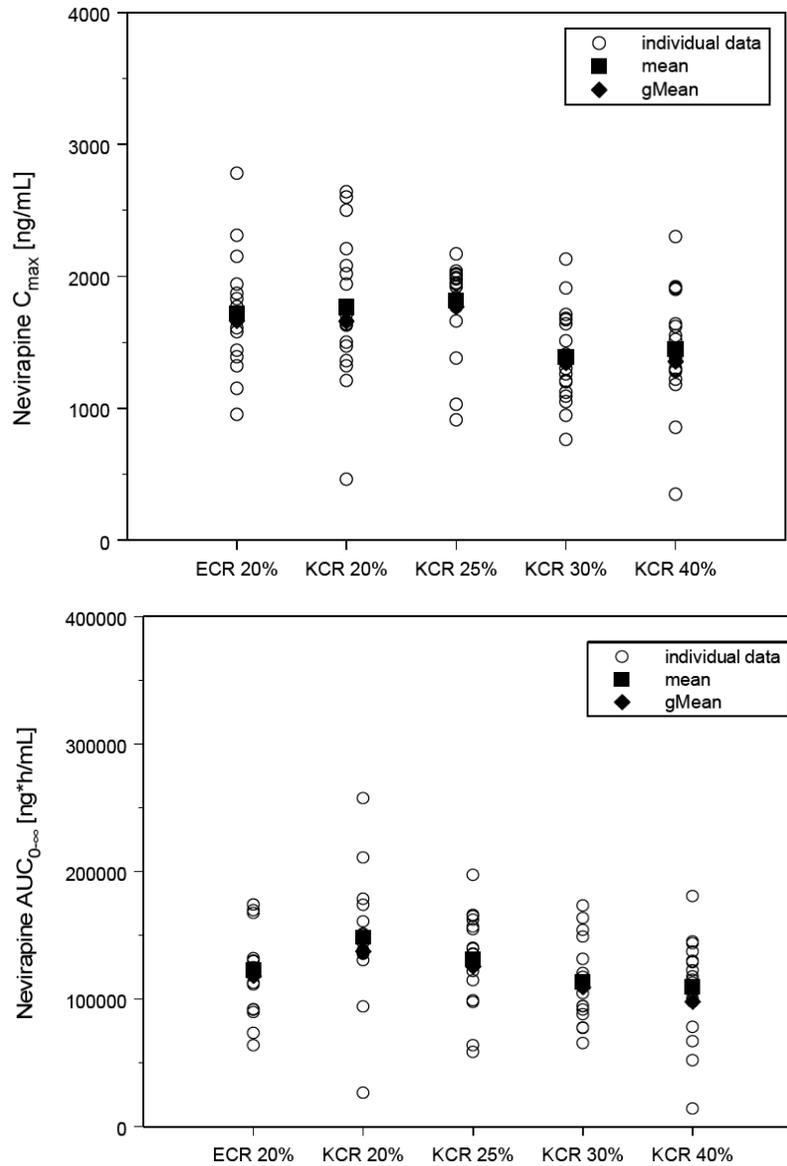


Fig 3 shows the distribution of the individual C_{max} and $AUC_{0-\infty}$ of nevirapine by dose (400 mg) and various extended release formulations

Fig 3: Distribution of the individual C_{max} and $AUC_{0-\infty}$ of nevirapine by dose (400 mg) and various extended release formulations

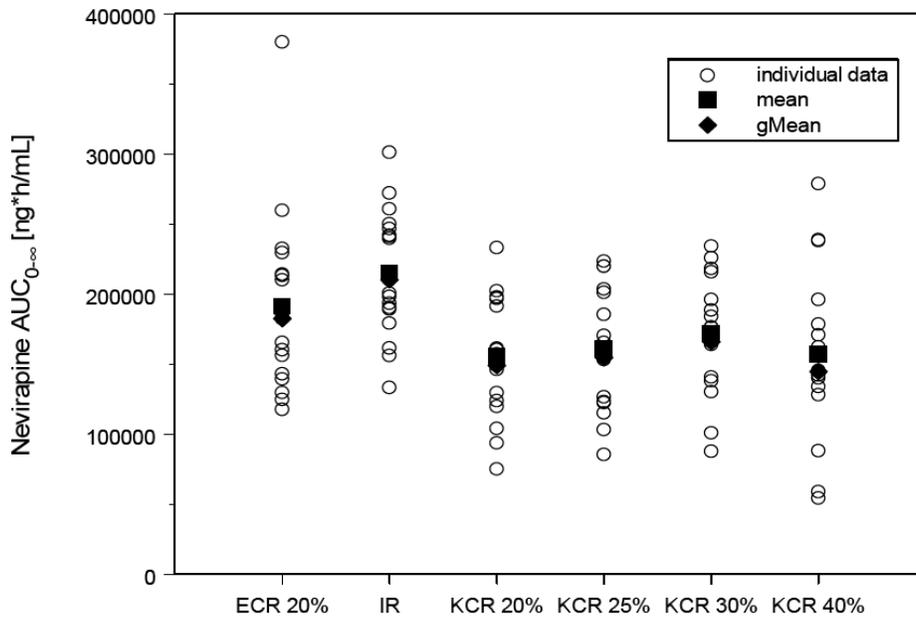
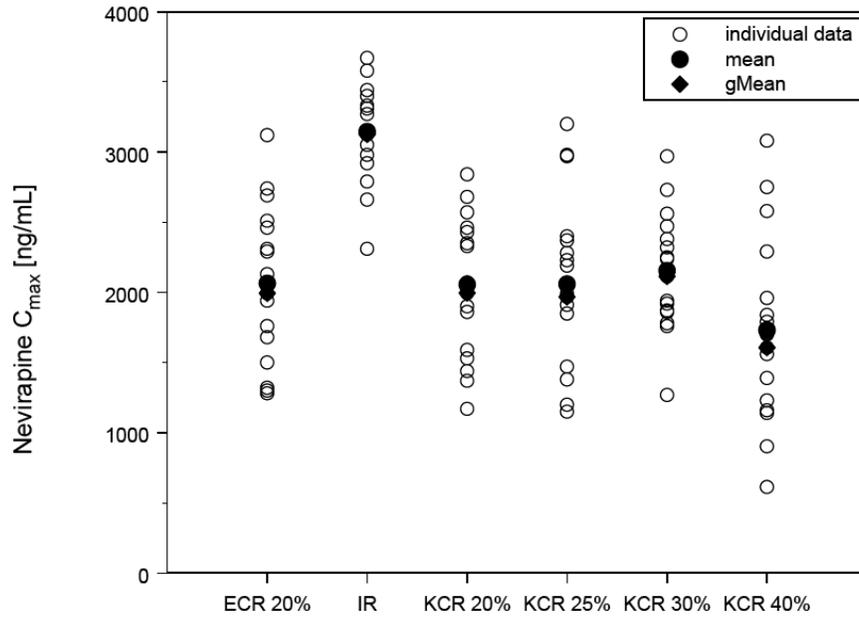


Table 5 shows the evaluation of the relative bioavailability (nevirapine 400 mg IR formulation is reference formulation) of the various extended release formulations.

Table 5: Evaluation of the relative bioavailability (nevirapine 400 mg IR formulation is reference formulation) of the various extended release formulations

Nevirapine	N	Inter-ind. gCV [%]	gMean Ratio (Test:Ref.) [%]	90% CI	
				Lower Limit [%]	Upper Limit [%]
AUC_{0-∞} dose normalised [ng·h/mL/mg]					
300 ECR20%	17	36.7	74.8	61.2	91.5
300 KCR20%	17	36.7	87.1	71.2	107.0
300 KCR25%	17	36.7	79.6	65.1	97.4
300 KCR30%	17	36.7	69.3	56.6	84.8
300 KCR40%	17	36.7	62.1	50.7	75.9
400 ECR20%	17	36.7	86.8	70.9	106.0
400 KCR20%	17	36.7	70.9	57.9	86.7
400 KCR25%	17	36.7	73.6	60.1	90.0
400 KCR30%	17	36.7	78.9	64.5	96.6
400 KCR40%	17	36.7	68.8	56.2	84.2
200 IR	17	36.7	109	88.9	133
C_{max} dose normalised [ng/mL/mg]					
300 ECR20%	17	30.3	71.0	60.0	84.0
300 KCR20%	17	30.3	70.8	59.8	83.7
300 KCR25%	17	30.3	75.5	63.8	89.3
300 KCR30%	17	30.3	57.3	48.4	67.8
300 KCR40%	17	30.3	57.8	48.8	68.3
400 ECR20%	17	30.3	63.8	53.9	75.5
400 KCR20%	17	30.3	63.8	53.9	75.5
400 KCR25%	17	30.3	63.0	53.2	74.5
400 KCR30%	17	30.3	67.7	57.2	80.0
400 KCR40%	17	30.3	51.4	43.5	60.8
200 IR	17	30.3	112	94.3	132
C₂₄ dose normalised [ng/mL/mg]					
300 ECR20%	17	34.0	88.7	73.5	106.9
300 KCR20%	17	34.0	87.9	72.9	106.0
300 KCR25%	17	34.0	92.8	77.0	111.9
300 KCR30%	17	34.0	67.6	56.0	81.5
300 KCR40%	17	34.0	67.9	56.3	81.9
400 ECR20%	17	34.0	77.8	64.5	93.8
400 KCR20%	17	34.0	80.3	66.6	96.8
400 KCR25%	17	34.0	74.8	62.0	90.2
400 KCR30%	17	34.0	75.6	62.7	91.2
400 KCR40%	17	34.0	62.6	51.9	75.5
200 IR	17	34.0	99.6	82.6	120.2

Source data: Table 15.5.3: 2

The geometric mean test/reference ratios of AUC_{0-∞} ranged between 62.1 and 87.1 % for nevirapine ER 300 mg and between 68.8 and 86.8 % for nevirapine ER 400 mg formulations.

CONCLUSION

All the NVP XR formulations evaluated showed lower BA after single dose administration compared with NVP IR 400 mg (2 X 200 mg). Based on the

results of the trial, two prototypes (KCR 25 % and KCR 20 %) at 300 mg and 400 mg were selected for further evaluation.

APPEARS THIS WAY ON ORIGINAL.

Study Number

1100.1489

Title

Steady state bioavailability of 2 different nevirapine extended release formulations compared to steady state 400 mg of Viramune (200 mg BID) in HIV-1 infected subjects, an open label, non-randomized, multiple-dose and multi-stage parallel group study.

Objectives

- Investigate the steady state bioavailability of two different NVP XR formulations at 300 mg or 400 mg QD in comparison with the commercially available NVP immediate release (IR) tablet at 200 mg BID (400 mg/day)
- Assess the effect of food on the rate and extent of absorption of the NVP XR formulation (steady state bioavailability of the NVP XR formulation administered after a meal was compared with the NVP XR formulation given under fasted conditions)

Study Design

Phase Ib open-label, multi-dose, and multi-stage parallel-group study to assess the steady state bioavailability of two different NVP XR formulations in HIV-1 infected patients who were on a NVP IR treatment for at least 12 weeks. The trial duration was planned for 7 weeks, including a treatment period of 22 days (after screening, PK parameters of NVP IR were tested over 3 days, the following 19 days were to test the PK parameters of NVP XR).

Subjects maintained for at least 12 weeks on a Viramune[®] IR based antiretroviral treatment without PIs (allowed in treatment history) and undetectable viral load (< 50 copies/mL) were eligible for the trial. After screening, subjects were switched from Viramune[®] IR to one of two NVP XR formulations at a dose of 300 mg or 400 mg QD for 19 days. Blood samples were collected prior to the morning doses of NVP IR on Day 1 and Day 2 for measurement of trough NVP concentrations of the reference therapy. On Day 3, NVP IR was administered under fasted conditions and serial blood samples were collected over 24 hours to determine the plasma concentration of NVP. Subsequently, NVP IR treatment was stopped after the last intake on Day 3.

Subjects were switched to NVP XR at Day 4 in the morning and were allocated to the trial to one of the four test arms in the order of their entry. The blood samples were collected prior to the morning doses of NVP XR from Day 15 to Day 17 for measurement of trough NVP concentrations of the various test treatments. On

Day 18, serial blood samples were collected over 24 hours to determine the PK of NVP of the various test treatments under fasting conditions.

To evaluate the impact of food on plasma concentrations of NVP of the test treatments, the XR doses were administered with a high fat breakfast on days 19, 20, 21, and 22. The administration of NVP XR was stopped after dose on Day 22. Subjects were switched back to the NVP IR treatment as taken before entering the study. All subjects were to attend an end of trial (EOT) visit within two weeks after the last study assessment.

In order to prevent treatment failure, the PK parameters for the 400 mg dose of both the XR formulations (KCR 20 % and KCR 25 %) were assessed before evaluating the lower (300 mg) dose.

Rationale for Dose Selection

Two dose strengths (300 mg and 400 mg) of five different NVP XR formulations were studied along with immediate release tablets in an open label, single dose, parallel group, non-randomized trial in 204 healthy volunteers (1100.1485). Based on the results of trial 1100.1485, NVP XR formulations with two different hypromellose controlled release (KCR) formulations (KCR 25 % and KCR 20 %) were selected for this trial (trial 1100.1489).

Investigational Products

Table 1 shows the various formulations investigated in the trial.

Table 1: Various formulations investigated in the trial

Test Formulation / Arm	Substance, Unit Strength, Designation	Batch Number	Medication number	Route of administration	Posology	Source
1 / A	NVP XR 400 mg (KCR 25%)	B063000006	1001 - 1048	p.o.	1-0-0	BIPI
2 / B	NVP XR 400 mg (KCR 20%)	B063000109	1101 - 1148	p.o.	1-0-0	BIPI
3 / C	NVP XR 300 mg (KCR 25%)	B063000004	1201 - 1248	p.o.	1-0-0	BIPI
4 / D	NVP XR 300 mg (KCR 20%)	B063000053	1301 - 1348	p.o.	1-0-0	BIPI
Reference therapy	NVP IR 200 mg (Viramune®)	Commercial product	None	p.o.	1-0-1	Local

Pharmacokinetic Sampling Schedule and Determination of Plasma Concentration of NVP

Sampling Schedule

The trough (morning) samples were collected on days 1, 2, 3 (pre-dose), 4 (pre-dose), 15, 16, 17, 18 (pre-dose), 19 (pre-dose), 21, 22 (pre-dose) and 23 (pre-dose). The intensive PK sampling after administration of the IR dose was conducted (over 2 dosing intervals) at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 (pre-dose), 12.5, 13, 14, 15, 17, 20, and 24 hours. The intensive PK sampling for the XR formulations under fasted conditions on day 18 after the morning dose was conducted at the following time points: pre-dose, 1, 3, 5, 7, 10, 12, 14, 16, 18, 20, 22, and 24 hours. The intensive PK sampling for the XR formulations under fed conditions was conducted on day 22 after the morning dose at the following time points: pre-dose, 1, 3, 5, 7, 10, 12, 14, 16, 18, 20, 22, and 24 hours.

Determination of Plasma Concentration of NVP

The plasma concentration of NVP was determined by a validated HPLC-MS/MS method. The details of the assay methodology are presented in table 2 below.

Table 2: Details of assay methodology

		Precision (%)	Accuracy (%)
LLOQ Calibration Standards			
	Inter-batch	6.05	-0.729
	Intra-batch	9.69	-1.70
ULOQ Calibration Standards			
	Inter-batch	2.52	-0.839
	Intra-batch	3.86	-2.09
Quality Control Samples			
Inter-batch	LLOQ	11.7	-1.34
	Low	6.51	3.09
	Medium	5.46	0.743
	High	5.62	4.46
Intra-batch	LLOQ	20.1 (7.67)*	-2.50 (-10.2)*
	Low	7.35	6.50
	Medium	6.87	3.61
	High	7.23	6.47

* Numbers in parentheses indicate maximum intra-assay precision or accuracy value after exclusion of Dixon outliers.

Source data: [U06-3155](#)

Pharmacokinetic Analysis

The PK parameters $AUC_{T,ss}$, $C_{min,ss}$, and $C_{max,ss}$ were to be log-transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for log(T)-log(R) was to be estimated by the difference in the corresponding Least Square Means (point estimate). Two-sided 90% confidence intervals based on the t-distribution were computed. These quantities were then to be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates between response under Test and response under Reference.

RESULTS

Table 3 shows the demographics of the patients enrolled in the trial.

Table 3: Demographics of the patients enrolled in the trial.

	NVP XR 300 mg KCR 20% N=23	NVP XR 300 mg KCR 25% N=21	NVP XR 400 mg KCR 20% N=24	NVP XR 400 mg KCR 25% N=24	Total N=92
Sex					
Male	17 (73.9)	19 (90.5)	21 (87.5)	22 (91.7)	79 (85.9)
Female	6 (26.1)	2 (9.5)	3 (12.5)	2 (8.3)	13 (14.1)
Age [years]					
Mean (SD)	41.3 (8.8)	41.2 (7.7)	44.0 (8.4)	45.2 (7.9)	43.0 (8.3)
Range	28 to 62	26 to 65	24 to 56	29 to 62	24 to 65
Age group					
<60 years	21 (91.3)	20 (95.2)	24 (100.0)	22 (91.7)	87 (94.6)
≥60 years	2 (8.7)	1 (4.8)	0 (0.0)	2 (8.3)	5 (5.4)
Race*					
Not recorded	1 (4.3)	6 (28.6)	0 (0.0)	0 (0.0)	7 (7.6)
White	18 (78.3)	14 (66.7)	22 (91.7)	24 (100.0)	78 (84.8)
Black	3 (13.0)	1 (4.8)	2 (8.3)	0 (0.0)	6 (6.5)
Asian	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Height [cm]					
Mean (SD)	174.8 (7.8)	177.3 (8.6)	176.0 (7.5)	177.3 (7.9)	176.3 (7.9)
Range	156 to 188	159 to 196	162 to 192	167 to 196	156 to 196
Weight [kg]					
Mean (SD)	75.7 (11.7)	70.6 (10.4)	71.8 (10.5)	74.0 (11.6)	73.1 (11.1)
Range	45 to 95	49 to 93	53 to 92	75 to 107	45 to 107
Body mass index [kg/m ²]					
Mean (SD)	24.704 (3.103)	22.357 (2.020)	23.158 (3.001)	23.450 (2.481)	23.438 (2.784)
Range	18.50 to 30.00	19.40 to 26.20	18.10 to 29.80	18.70 to 28.70	18.10 to 30.00
Smoking status					
Never smoked	12 (52.2)	5 (23.8)	12 (50.0)	6 (25.0)	35 (38.0)
Ex-smoker	3 (13.0)	6 (28.6)	2 (8.3)	5 (20.8)	16 (17.4)
Currently smokes	8 (34.8)	10 (47.6)	10 (41.7)	13 (54.2)	41 (44.6)
Alcohol history					
Non-drinker	10 (43.5)	4 (19.0)	5 (20.8)	8 (33.3)	27 (29.3)
Average cons.	13 (56.5)	17 (81.0)	19 (79.2)	16 (66.7)	65 (70.7)

*Race was not recorded in France.

Source: [Table 15.1.4: 1](#)

PHARMACOKINETICS

Fig 1 shows the mean nevirapine plasma concentration-time profiles after oral administration of NVP XR 400 mg KCR 25 %.

Fig 1: Mean nevirapine plasma concentration-time profiles after oral administration of NVP XR 400 mg KCR 25 %

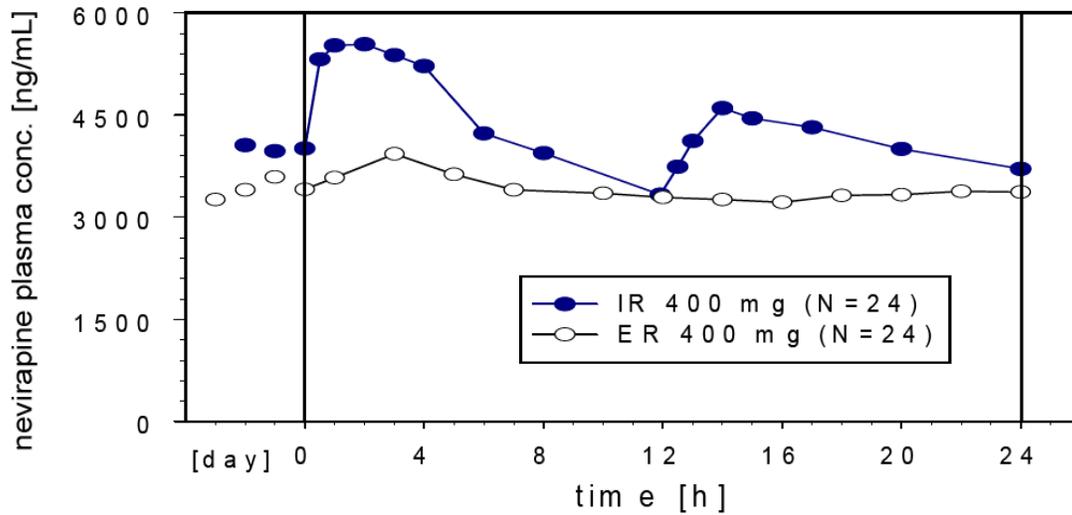


Fig 2 shows the mean nevirapine plasma concentration-time profiles after oral administration of NVP XR 400 mg KCR 20 %.

Fig 2: Mean nevirapine plasma concentration-time profiles after oral administration of NVP XR 400 mg KCR 20 %

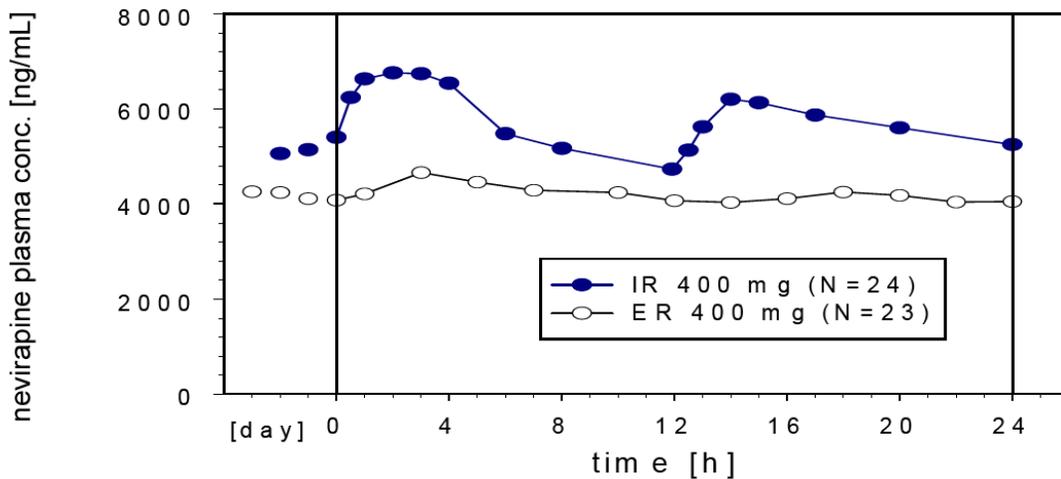


Table 4 shows the summary of the pharmacokinetic parameters of nevirapine after oral administration of NVP XR 400 mg formulations and NVP IR (2 X 200 mg) formulation

Table 4: Summary of the pharmacokinetic parameters of nevirapine after oral administration of NVP XR 400 mg formulations and NVP IR (2 X 200 mg) formulation

Parameter	Units		Treatment A			Treatment B		
			NVP XR 400 mg KCR 25%			NVP XR 400 mg KCR 20%		
			IR	XR	XR	IR	XR	XR
				fasted	fed		fasted	fed
		(N=24)	(N=24)	(N=24)	(N=24)	(N=23)	(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	5950	4140	5010	7340	4850	6230
		(%CV)	(26.8)	(22.4)	(25.6)	(33.9)	(42.3)	(31.8)
		gMean	5750	4040	4850	7000	4470	5980
$C_{min,ss}$	[ng/mL]	mean	3240	2920	3150	4500	3600	4010
		(%CV)	(30.9)	(32.3)	(27.7)	(40.0)	(49.0)	(43.8)
		gMean	3090	2770	3030	4220	3190	3680
$C_{max,ss}/C_{min,ss}$		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	4280	3420	4030	5690	4220	5140
		(%CV)	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	4140	3290	3900	5390	3860	4880
$AUC_{\tau,ss}$	[ng·h/mL]	mean	103000	82000	96700	137000	101000	123000
		(%CV)	(26.2)	(27.1)	(25.0)	(36.4)	(43.6)	(35.5)
		gMean	99400	79000	93700	129000	92700	117000
$AUC_{\tau,ss,5}/AUC_{\tau,ss,6}$		mean	1.08	---	---	1.02	---	---
		(%CV)	(11.8)			(8.69)		
		gMean	1.08	---	---	1.02	---	---
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

Source data: [Table 15.6.2.1: 1 to Table 15.6.2.1: 6](#)

Table 5 shows the summary of the pharmacokinetic parameters of nevirapine after oral administration of NVP XR 300 mg formulations and NVP IR (2 X 200 mg) formulation

Table 5: Summary of the pharmacokinetic parameters of nevirapine after oral administration of NVP XR 300 mg formulations and NVP IR (2 X 200 mg) formulation

Parameter	Units		Treatment C			Treatment D		
			NVP XR 300 mg KCR 25%			NVP XR 300 mg KCR 20%		
			IR	XR	XR	IR	XR	XR
				fasted	fed		fasted	fed
		(N=21)	(N=21)	(N=21)	(N=23)	(N=23)	(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	6090	3580	4270	6330	3560	4600
		(%CV)	(22.1)	(30.4)	(47.3)	(25.9)	(25.2)	(29.6)
		gMean	5960	3450	3890	6150	3460	4430
$C_{min,ss}$	[ng/mL]	mean	3250	2370	2640	3650	2300	2670
		(%CV)	(35.4)	(28.1)	(53.8)	(34.5)	(33.0)	(36.5)
		gMean	3050	2290	2300	3480	2180	2520
$C_{max,ss}/C_{min,ss}$		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	4300	2920	3420	4700	2940	3590
		(%CV)	(25.1)	(29.3)	(48.0)	(29.6)	(25.9)	(28.7)
		gMean	4180	2820	3100	4530	2840	3460
$AUC_{\tau,ss}$	[ng·h/mL]	mean	103000	70100	82100	113000	70600	86100
		(%CV)	(25.1)	(29.3)	(48.0)	(29.6)	(25.9)	(28.7)
		gMean	100000	67700	74500	109000	68200	83000
$AUC_{\tau,ss_5}/AUC_{\tau,ss_6}$		mean	1.13	---	---	1.09	---	---
		(%CV)	(16.4)			(7.02)		
		gMean	1.12	---	---	1.09	---	---
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

Source data: [Table 15.6.2.1: 7 to Table 15.6.2.1: 12](#)

EVALUATION OF THE RELATIVE BIOAVAILABILITY OF THE NVP XR FORMULATION

Table 6 shows the computation of the relative bioavailability of NVP XR formulations administered under *fasted* conditions versus NVP IR 400 mg

Table 6: Computation of the relative bioavailability of NVP XR formulations administered under *fasted* conditions versus NVP IR 400 mg

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC _{t,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	79.5	73.0	86.7
400 mg KCR 20%	23/23	23.5	71.0	63.3	79.7
300 mg KCR 25%	20/20	22.1	90.3	80.4	101.4
300 mg KCR 20%	23/23	14.5	83.7	77.9	89.9
C _{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	70.2	64.6	76.3
400 mg KCR 20%	23/23	23.3	63.7	56.8	71.4
300 mg KCR 25%	20/20	22.6	77.0	68.3	86.7
300 mg KCR 20%	23/23	16.4	74.9	69.1	81.2
C _{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	89.6	80.6	99.6
400 mg KCR 20%	23/23	29.2	75.1	65.1	86.5
300 mg KCR 25%	20/20	32.0	99.4	84.2	117.4
300 mg KCR 20%	23/23	16.4	83.5	77.0	90.5

Source data: [Tables 15.5.1: 2, 15.5.1: 4, 15.5.1: 6, 15.5.1: 8, 15.5.1: 10, 15.5.1: 12, 15.5.1: 14, 15.5.1: 16, 15.5.1: 18, 15.5.1: 20, 15.5.1: 22, 15.5.1: 24](#)

Table 7 shows the computation of the relative bioavailability of NVP XR formulations administered under *fed* conditions versus NVP IR 400 mg

Table 7: Computation of the relative bioavailability of NVP XR formulations administered under *fed* conditions versus NVP IR 400 mg

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC_{t,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	94.3	86.5	102.8
400 mg KCR 20%	23/23	23.5	89.7	80.0	100.6
300 mg KCR 25%	20/20	22.1	97.9	87.1	110.0
300 mg KCR 20%	23/23	14.5	101.7	94.7	109.3
C_{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	84.4	77.6	91.7
400 mg KCR 20%	23/23	23.3	85.2	76.1	95.5
300 mg KCR 25%	20/20	22.6	85.7	76.1	96.5
300 mg KCR 20%	22/23	16.4	96.8	89.2	105.1
C_{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	98.2	88.4	109.1
400 mg KCR 20%	23/23	29.2	86.6	75.1	99.8
300 mg KCR 25%	20/20	32.0	99.2	84.0	117.1
300 mg KCR 20%	23/23	16.4	96.5	89.0	104.6

Source data: [Tables 15.5.3: 1 to 15.5.3: 12](#)

Table 8 shows the computation of the relative bioavailability of NVP XR formulations administered under fasted vs fed conditions

Table 8: Computation of the relative bioavailability of NVP XR formulations administered under fasted vs fed conditions

Parameter, Unit Formulation	N	Intra-individual gCV [%]	gMean Ratio (Test:Ref) [%]	90% Confidence interval	
				Lower limit [%]	Upper limit [%]
AUC_{t,ss} [ng•h/mL]					
400 mg KCR 25%	24/24	17.9	118.5	108.8	129.2
400 mg KCR 20%	23/23	23.5	126.3	112.6	141.7
300 mg KCR 25%	20/20	22.1	108.4	96.5	121.8
300 mg KCR 20%	23/23	14.5	121.6	113.2	130.6
C_{max,ss} [ng/mL]					
400 mg KCR 25%	24/24	17.4	120.2	110.6	130.7
400 mg KCR 20%	23/23	23.3	133.8	119.4	150.0
300 mg KCR 25%	20/20	22.6	111.4	98.9	125.4
300 mg KCR 20%	22/23	16.4	129.3	119.1	140.3
C_{min,ss} [ng/mL]					
400 mg KCR 25%	24/24	22.0	109.6	98.6	121.8
400 mg KCR 20%	23/23	29.2	115.3	100.0	132.9
300 mg KCR 25%	20/20	32.0	99.8	84.5	117.8
300 mg KCR 20%	23/23	16.4	115.5	106.6	125.3

Source data: [Tables 15.5.2: 1 to 15.5.2: 12](#)

The geometric mean test/reference ratios of AUC_{t,ss} for nevirapine were 79.5 % and 71.0 % with NVP XR 400 mg KCR 25 % and KCR 20 % formulations, respectively, and 90.3 % and 83.7 % with NVP XR 300 mg KCR 25 % and KCR

20 % formulations, respectively. Administration of NVP XR with food resulted in increased relative bioavailability of NVP compared with NVP IR. The relative bioavailability of nevirapine, assessed by geometric mean test/reference ratios of $AUC_{T,ss}$, $C_{max,ss}$ and $C_{min,ss}$, with NVP XR KCR 20 % formulations appeared consistently slightly lower than that with KCR 25 % formulations at both doses when administered in the fasted state.

CONCLUSION

Based on the results of the trial, NVP XR 400 mg KCR 25 % was selected for further development.

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/s/

VIKRAM ARYA
02/25/2011

SARAH M ROBERTSON
02/25/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-152 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DAP		
Sponsor:	Boehringer Ingelheim	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Viramune XR	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Nevirapine Extended Release Tablets, 400 mg	Date Assigned:	Jun 16, 2010
Indication:	In combination with other antiretroviral agents for the treatment of HIV-1 infection	Date of Review:	Feb 10, 2011
Formulation/strengths	Extended Release tablets, 400 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
June 3, 2010 Aug 12, 2010 Oct 29, 2010	June 3, 2010	June 16, 2010	April 3, 2011
Type of Submission:	Original NDA		
Type of Consult:	IVIVC model/Dissolution method and specifications/in vitro alcohol interaction study		
REVIEW SUMMARY:			
<p>Viramune[®] (Nevirapine) 200 mg immediate release tablets were approved by the Agency on June 21, 1996 under NDA 20-636. It is indicated for the combination antiretroviral treatment of HIV-1 infection. The recommended dose for Viramune is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents.</p> <p>The sponsor has developed a new formulation for Nevirapine consisting of an extended release tablet for the once daily treatment of HIV-1 infection. The proposed regimen is 400 mg QD. The clinical development program for this new drug formulation for the proposed indication included 3 Phase I studies and 2 Phase III studies. The results of one clinical pharmacology study were utilized for the construction of a Level A in vivo in vitro correlation (IVIVC) for Nevirapine ER, 400 mg tablets.</p> <p>The Level A IVIVC was developed using data from 3 formulations (Nevirapine ER KCR 25%, 30% and 40%) which were manufactured so as to exhibit different release rates as demonstrated by in vitro release tests using USP apparatus type I, 75 rpm. Tablet dissolution was carried out in the proposed QC medium (900 mL of media, 0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate). Data from oral administration of Nevirapine ER KCR 20% Formulation was used to provide an estimate of unit impulse response (UIR). The analyses were performed using the IVIVC ToolkitTM for WinNonlin[®]. Mean data were used to build a correlation as the in vivo study in humans was carried out by parallel design. The procedure for developing the IVIVC followed a two stage approach (deconvolution followed by convolution). The IVIVC model was internally validated using data utilized in the construction of the model. The model was also externally validated upon the Agency's request using data from a formulation not used in the construction of the IVIVC.</p> <p>Under the model assumptions, % error and the MAPPE for the C_{max} and AUC_t values met the internal</p>			

and external predictability requirements; therefore it is acceptable and can be used to support future biowaiver applications. In the present submission, the IVIVC model is not being used to support any waiver request.

The dissolution method and specifications being proposed by the sponsor for Nevirapine ER Tablets is based on the in vitro performance of clinical batches, stability batches and IVIVC model as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Nevirapine	ER Tablets	USP Basket	75	0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate, 900 mL	Time % Label Claim Dissolved 2 hours :Not more than (b) (4) 8 hours: (b) (4) 20 hours: Not less than (b) (4)

This reviewer ran the IVIVC model using the WinNonLin IVIVC Toolkit to make predictions of the Cmax and AUC for the mean percentage dissolve (b) (4) variation. The mean in-vitro dissolution profile for the clinical and stability lots of Nevirapine ER Tablets, 400 mg was used as the target profile. The absolute % difference in predicted AUC and Cmax values corresponding to the high (b) (4) and low (b) (4) proposed dissolution specifications with respect to the target specification was lower than (b) (4). Therefore, the sponsor's proposed dissolution specifications for Nevirapine ER Tablets are acceptable as follows:

Proposed dissolution specifications for Nevirapine ER Tablets

	Mean in-vitro Profile	Proposed Specification (mean (b) (4) variation)
	Clinical Lots (%) Dissolution	% Dissolution
Hours		
2	14	No more than (b) (4)
8	54	(b) (4)
20	97	NLT (b) (4)

There were no signs of an uncontrolled drug release from the formulation of nevirapine ER tablets when dissolved in 4, 20 or 40% ethanol tested using either the QC method or HCl 0.1 N as the medium. On the contrary, the release profiles became slower in the presence of alcohol.

GastroPlus® software was utilized for simulating *in vitro* and *in vivo* behavior as a function of (b) (4)

(b) (4)

The

results of the simulations ran by the sponsor support this statement.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 201152 (000) submitted on June 3, 2010, Aug 12, 2010, and Oct 29, 2010. The proposed IVIVC model, dissolution method and specifications for Nevirapine ER tablets, 400 mg are acceptable. Therefore, we found this NDA acceptable from biopharmaceutics perspective.

Sandra Suarez Sharp, Ph. D.
 Biopharmaceutics Reviewer
 Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
 Biopharmaceutics Supervisor
 Office of New Drugs Quality Assessment

c.c. JDavid, ADorantes, SMiller, ShPagay

INTRODUCTION

Viramune[®] (Nevirapine) 200 mg immediate release tablets were approved by the Agency on June 21, 1996 under NDA 20-636. It is indicated for the combination antiretroviral treatment of HIV-1 infection. The recommended dose for Viramune is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents.

The sponsor has developed a new formulation for Nevirapine consisting of an extended release tablet for the once daily treatment of HIV-1 infection. The proposed regimen is 400 mg QD. The sponsor believes that this new formulation presents lower maximum plasma concentrations (C_{max}) and lower exposures (AUC) while maintaining a C_{min} at 3 µg/mL needed for efficacy. The clinical development program for this new drug formulation for the proposed indication included 3 Phase I studies and 2 Phase III studies. An in vitro alcohol interaction study is also included. The results of one clinical pharmacology study was utilized for the construction of a two Level A in vivo in vitro correlation (IVIVC), one for the 400 mg and one for the 300 mg strengths. This review is focused on the acceptability of the IVIVC model, dissolution method and specifications, and in vitro alcohol-drug interaction study.

CHEMISTRY

Nevirapine extended-release tablets, 400 mg are yellow, oval, biconvex tablets. The tablets are debossed with product identification “V04” on one side and the BI tower logo on the other side. The qualitative and quantitative compositions of nevirapine extended-release tablets, 400 mg are shown in Table 1.

Table 1. Qualitative and quantitative composition of nevirapine ER tablets, 400 mg

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

(b) (4)

Dissolution Method

The dissolution method being proposed by the sponsor for Nevirapine ER tables is as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium
Nevirapine	ER Tablets	USP Basket	75	0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate, 900 mL

It is noted that the proposed dissolution method is the same as that used in the construction of the IVIVC for Nevirapine ER Tablets.

Dissolution Method Development

The following criteria were considered in the choice of method conditions:

- Apparatus: (b) (4)
[Redacted]
Apparatus I (10-mesh basket) was selected (b) (4)

- Stirring Rate: 100 rpm USP <1088>; most common operating speed for Apparatus 1.

- Dissolution medium: (b) (4)
[Redacted]
An aqueous buffer system containing 0.04 M sodium phosphate at pH 6.8 was chosen to reflect the predominant environment that the tablet would encounter during GI passage particularly those conditions in the colon where *in vivo* absorption exhibited the slowest rate. To insure that the medium had sufficient capacity to dissolve 400 mg of drug substance in the standard 900 mL or media, the addition of a surfactant was necessary. SDS at 6% (w/v) provided adequate solubilization to maintain “sink” conditions during testing.

With the objective of developing a Level A point-to-point IVIVC for this formulation, it was recognized that some adjustment in the *in vitro* dissolution test conditions was required. (b) (4)

[Redacted] Iterative experiments identified three adjustments that suitably protracted the dissolution profiles, namely, a reduction in

stirring speed from 100 to 75 rpm, change from a 10-mesh to 40-mesh USP Apparatus I basket, and reduction of SDS concentration in the dissolution medium from 6% to 2%. Figure 1 shows a typical dissolution profile for Nevirapine ER tablets, 400 mg tested using these new proposed conditions.

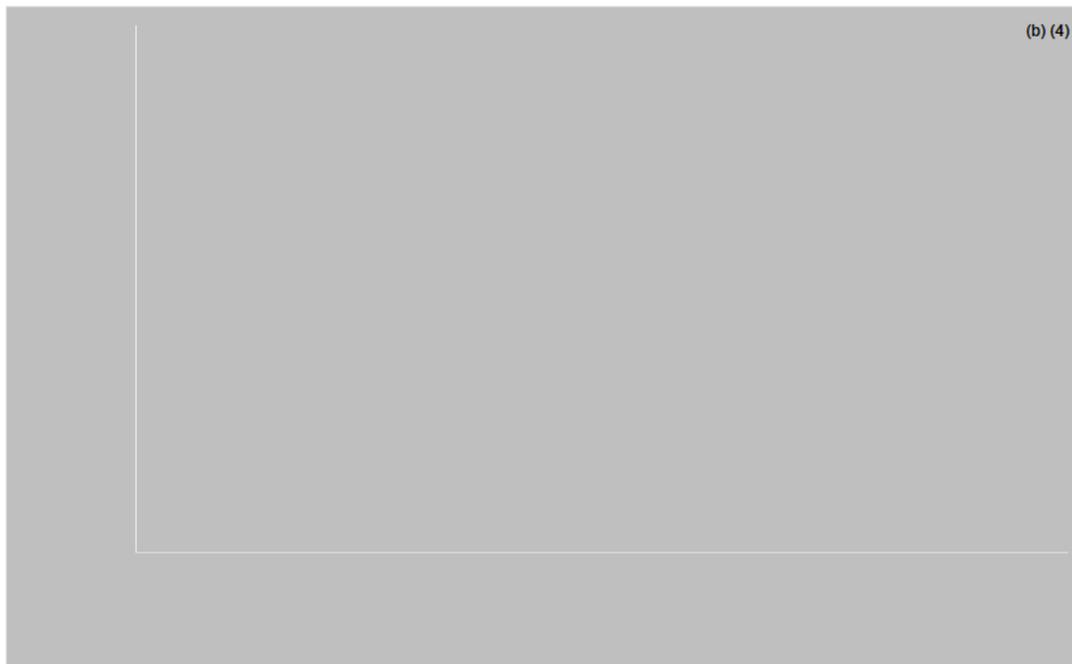


Figure 1. Composite plot of all data used in the justification of the dissolution acceptance criteria for nevirapine extended release tablets, 400 mg. L1 acceptance criteria at the 3 designated sample points are indicated by the horizontal reference lines.

IVIVC Model

The IVIVC model has been already reviewed¹. In summary a Double Weibull model with 1/Yobs weighting was used to fit mean *in vitro* data for all formulations. The Unit Impulse Response (UIR) was assessed using the KCR 20% formulation. Deconvolution of the mean *in vivo* concentration-time data was performed using the UIR to estimate *in vivo* drug release for all extended release formulations. The Level A correlation was developed to explain the relationship between *in vitro* dissolution data and *in vivo* absorption data. The best correlation was established using a linear model with a fixed cut off of 45 hrs. In addition to linear models, several non-linear models were also evaluated to develop an IVIVC. A total of 9 non-linear models were tested, including Quadratic, Cubic, Sigmoid, Weibull, Mitcherlish, and Logistic models. The internal predictability of the model for all formulations (400_K25, 400_K30, and 400_K40) used for the internal validation was within the acceptable limits. Figure 2 shows the exploratory plots (Fraction absorbed vs. Fraction dissolved) for the relationship between absorption and *in vitro* release). Figure 3 shows the *in vivo* concentration time profiles

¹ Biopharmaceutics review conducted by Dr. Arzu Selen for IND 74, 744 S 0014 entered in DARRTS on 07/09/08.

convolved using the mean in vitro dissolution data and the correlation model for the 400-mg ER tablets. Table 2 summarizes the results of the internal predictability.

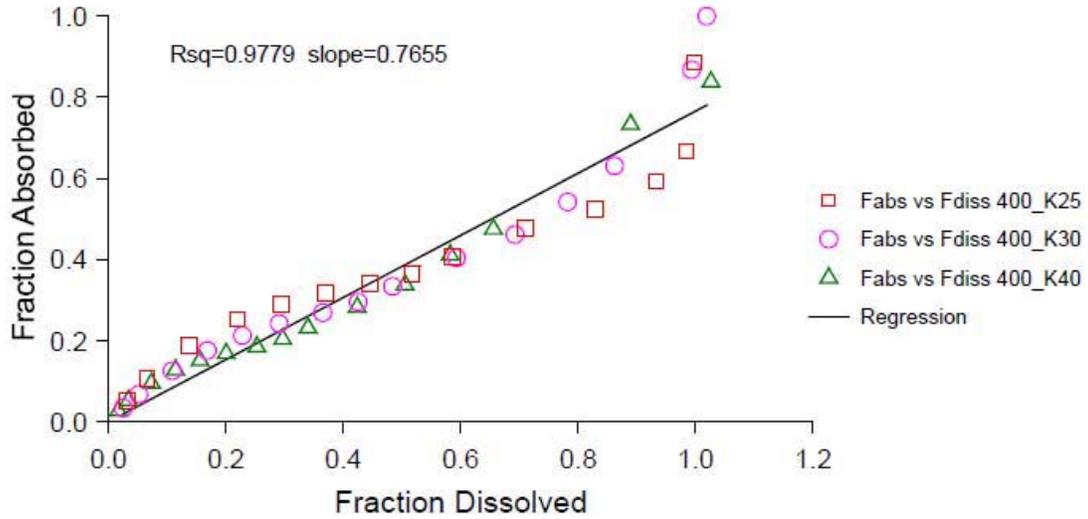
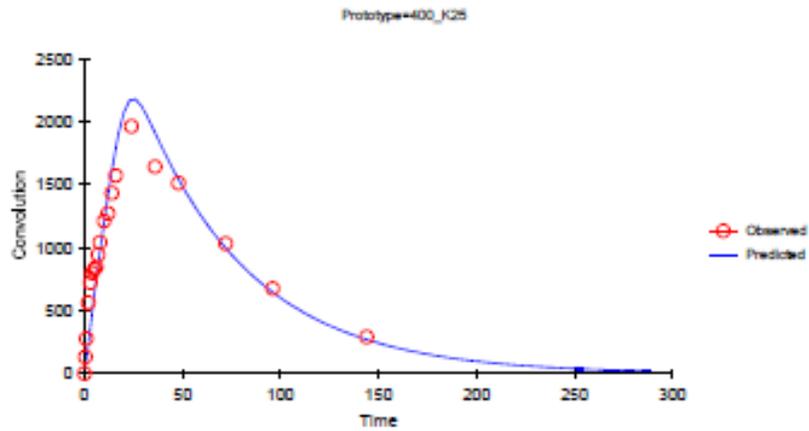


Figure 2. Exploratory plots for the relationship between dissolution and absorption for Nevirapine ER tablets 400 mg.



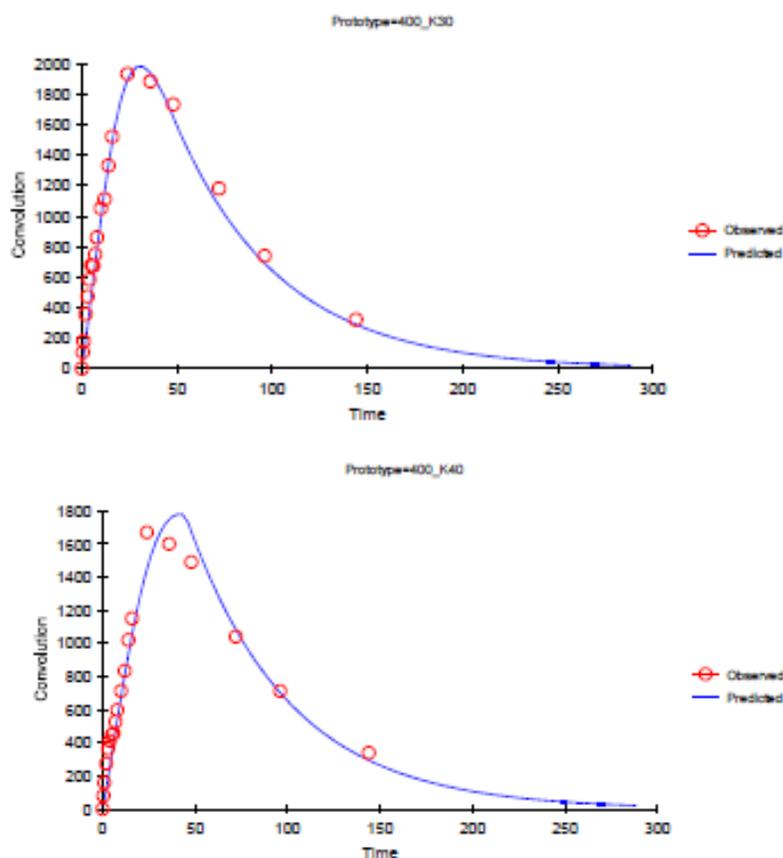


Figure 3. Observed and predicted plasma concentration time profiles convolved using the mean in vitro dissolution data and the correlation model for the 400-mg ER tablets.

Table 2. Summary of internal validation parameters for 400 mg nevirapine ER formulations

Parameter	Formulation	Predicted	Observed	%PE	Ratio
AUC _{0-tz} (ng-hr/mL)	400 K25	146095	142582	2.5	1.02
	400 K30	145143	152905	-5.1	0.95
	400 K40	134460	134152	0.2	1.00
	Average	141899	143213	2.6	0.99
C _{max} (ng/mL)	400 K25	2169	1960	10.7	1.11
	400 K30	1933	1930	0.2	1.00
	400 K40	1748	1670	4.6	1.05
	Average	1950	1853	5.2	1.05

Reviewer's Comments

It is noted however, that the formulations used in the construction of the IVIVC do not meet the requirements of being at least ^{(b) (4)} difference in terms of the in vitro and in vivo performance (see Figures 4-6). Dissolution profiles comparison of K25 vs K30 and K30 vs. K40 generated f₂ values higher than 50 (53 and 59, respectively). Figure 4 shows that formulations 400-K25 and 400-K30 have very similar absorption profile. Therefore, successful external predictability should had been provided for full application of the

IVIVC since only two of the three formulations used in the development of the IVIVC met the criteria of at least ^{(b) (4)} difference in *in vitro* release rate and systemic exposure.

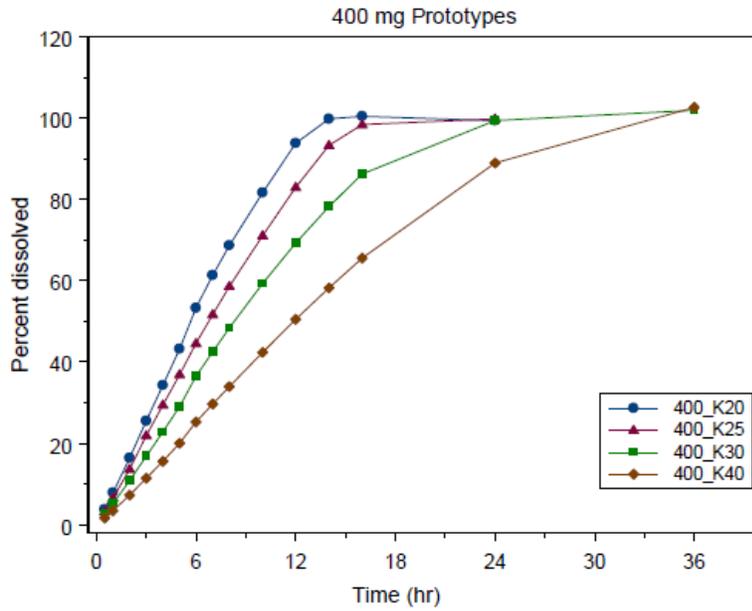


Figure 4. Mean *in vitro* dissolution profiles of nevirapine from 400 mg nevirapine extended release formulations.

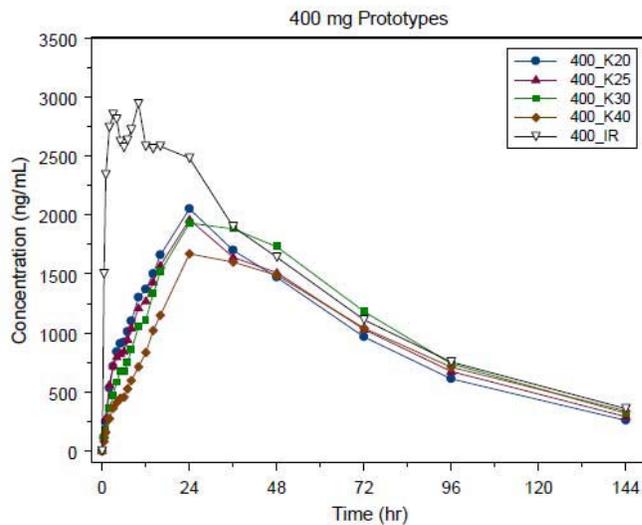


Figure 5. Mean *in vivo* concentration time profiles (0-144 h) of nevirapine following single oral administration of 400 mg nevirapine extended release formulations to healthy volunteers.

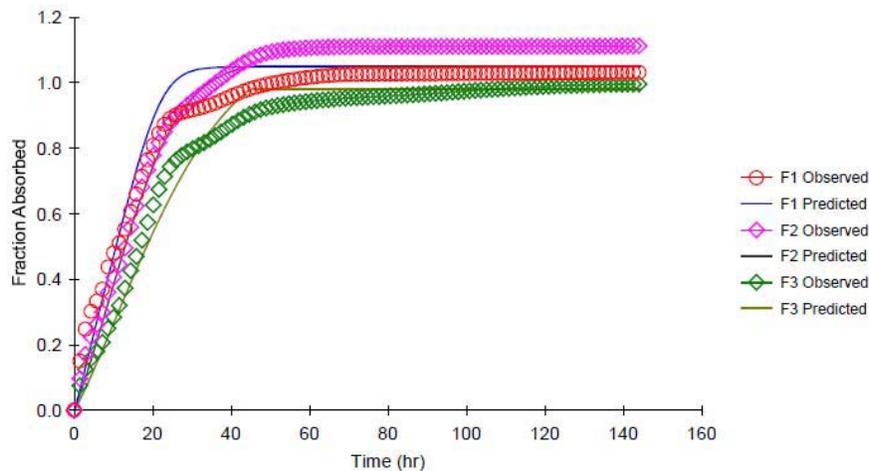


Figure 6. Predicted and observed Nevirapine fraction absorbed following single oral administration of 400 mg nevirapine extended release formulations to healthy volunteers.

Therefore, on July 30 2010 the sponsor was requested to provide the following information:

- *It is noted that only two of the formulations used in the construction of the proposed In Vitro/In Vivo Correlation (IVIVC) meet the requirements of showing at least a (b) (4) difference in both, the in vitro and in vivo performance. Specifically, we find that the dissolution profiles for K25 vs. K30 and for K30 vs. K40 were similar (f2 values were 53 and 59, respectively). Therefore, you will need to conduct an external predictability analysis of the model in order for you to implement your proposed IVIVC. Otherwise, your proposed IVIVC will only be limited to Category 2a applications (refer to Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlation).*

On August 12, 2010 the sponsor provided a complete response of the requested information as follows:

For the purpose of the external validation a 400 mg NVP XR formulation (Lot no. 079136) with 25% polymer content, evaluated in the 1100.1517 trial was selected. This formulation has “the same or similar release rate, but involving some change in manufacture of this batch (e.g. composition, process, equipment, manufacturing site)” as summarized in Table 3.

Table 3. Comparison of manufacturing differences between lots PD-2705 and 079136

Lot No.	PD-2705 (original IVIVC lot)	079136 (new external validation lot)
Manufacturing site	BI Pharmaceuticals Inc. R&D Clinical Manufacturing Ridgefield, CT	BI Roxane Laboratories, Inc. Proposed Commercial Manufacturing Columbus, OH
Composition	(b) (4)	
Batch Scale		
Process/ Equipment		
(b) (4)		

In vitro dissolution data were generated with the same method used earlier for developing the IVIVC. The similarity factor (f_2) was >50 for these two lots. The mean profile is shown in Figure 7. Table 4 summarizes the results of the external validation.

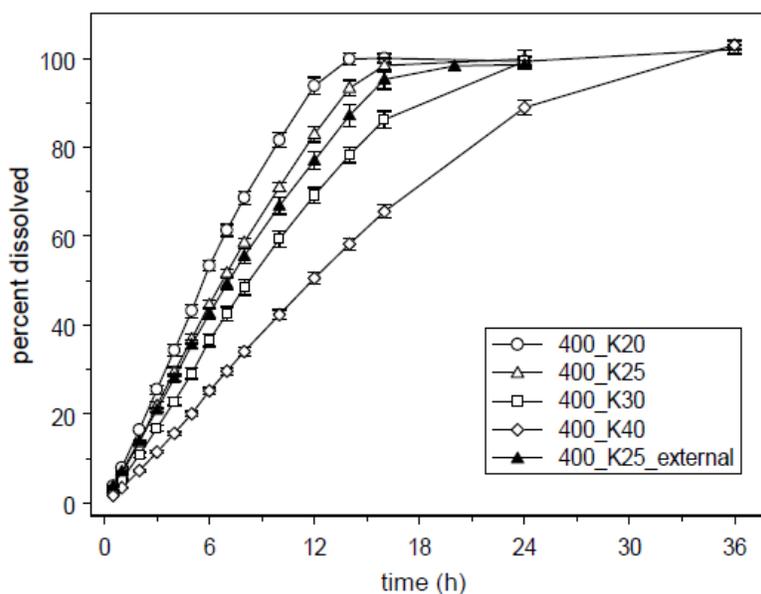


Figure 7. Mean (\pm SD) *in vitro* dissolution profiles of nevirapine from 400 mg nevirapine extended release formulations.

Table 4. Summary of external validation parameters for 400 mg nevirapine extended release formulations

Parameter	Formulation	Predicted	Observed	%PE	Ratio
AUC _{0-tz} (ng·hr/mL)	400 K25	144389	155889	7.4	0.93
C _{max} (ng/mL)	400 K25	2050	2080	1.5	0.99

Reviewer’s Conclusion

The predictability of the Level A IVIVC for 400 mg nevirapine ER formulations has been shown to be within the acceptable limits by both internal and external validation. Therefore, the established IVIVC can be used to support biowaiver applications.

PROPOSED SPECIFICATIONS

The sponsor proposed specifications for all strength of Nevirapine ER Tablets, 400mg are as follows:

Table 12. Sponsor’s proposed dissolution specifications

Acceptance criteria	
Time % Label Claim Dissolved	
2 hours :	Not more than (b) (4)
8 hours:	(b) (4)
20 hours:	Not less than (b) (4)

According to the sponsor, the proposed acceptance criteria are justified based upon statistical assessment of dissolution data acquired from multiple batches including batches used in clinical investigations. The established level A IVIVC model was applied to confirm that drug product batches with dissolution performance at the upper and lower boundaries of the specification would possess bioequivalent *in vivo* blood level profiles. The average dissolution profile is presented in Table 5.

Table 5. Average In-vitro Dissolution Profile for Nevirapine ER Tablets

Batch Type	Statistic	Hour 1	Hour 2	Hour 5	Hour 8	Hour 12	Hour 16	Hour 20	Hour 24
Clinical	Mean	7	14	35	53	74	89	97	99
	Range	(b) (4)							
Stability	Mean		14	36	55	75	90	97	100
	Range	(b) (4)							

Reviewer’s Comments

This reviewer ran the proposed IVIVC model under the same sponsor’s assumptions using WinNonLin IVIVC Toolkit to make predictions of the Cmax and AUC for the mean percentage dissolved ± (b) (4) variation. The mean in-vitro dissolution profile for the clinical and stability lots of Nevirapine ER Tablets, 400 mg was used as the target profile. The sponsor’s predicted values for Cmax and AUC are summarized on Table 6. Likewise, this reviewer’s predicted values are summarized on Table 7.

Table 6. C_{max} and AUC_{0-tz} ratios based on the mean % dissolution of the proposed marketed formulation at the proposed upper and lower limits of the dissolution specification.

Treatment	C _{max} [ng/mL]			AUC _{0-tz} [ng·h/mL]		
	Observed	Predicted	Ratio	Observed	Predicted	Ratio
Upper limits						(b) (4)
Lower limits						

Table 7. Predicted PK parameters (C_{max} and AUC) using the IVIVC model

PK Parameter	C _{max} (ng/mL)		AUC _t (ng*hr/mL)	
	Predicted	Absolute % difference To target	Predicted	% difference To target
Target				
Target	(b) (4)			
Target				
Sponsor's Low	(b) (4)			
Sponsor's High				
Absolute % difference between the Low and High values				
	Predicted	Absolute % difference	Predicted	% difference

Figure 8 shows the predicted dissolution profiles considering the dissolution profile for the target formulation, target formulation (b) (4) variation. Likewise, Figure 9 shows the predicted concentration-time profiles considering dissolution profiles of target (b) (4) variation. The results indicated that the absolute % difference in predicted C_{max} and AUC values corresponding to the high proposed dissolution specification (b) (4) with respect to the low specification (b) (4) were (b) (4) respectively (Table 7).

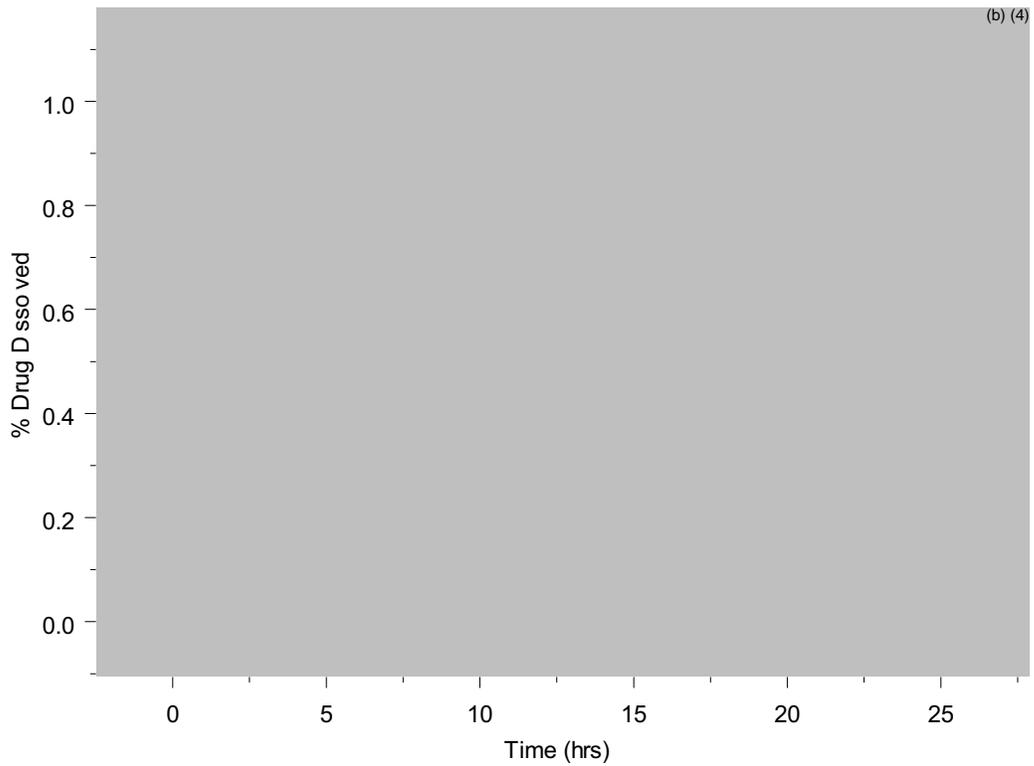


Figure 8. Predicted mean dissolution profiles using the Weibull model for the target formulation and target formulation \pm (b) (4) variation (generated using WinNonLin IVIVC Toolkit based on sponsor's provided data).

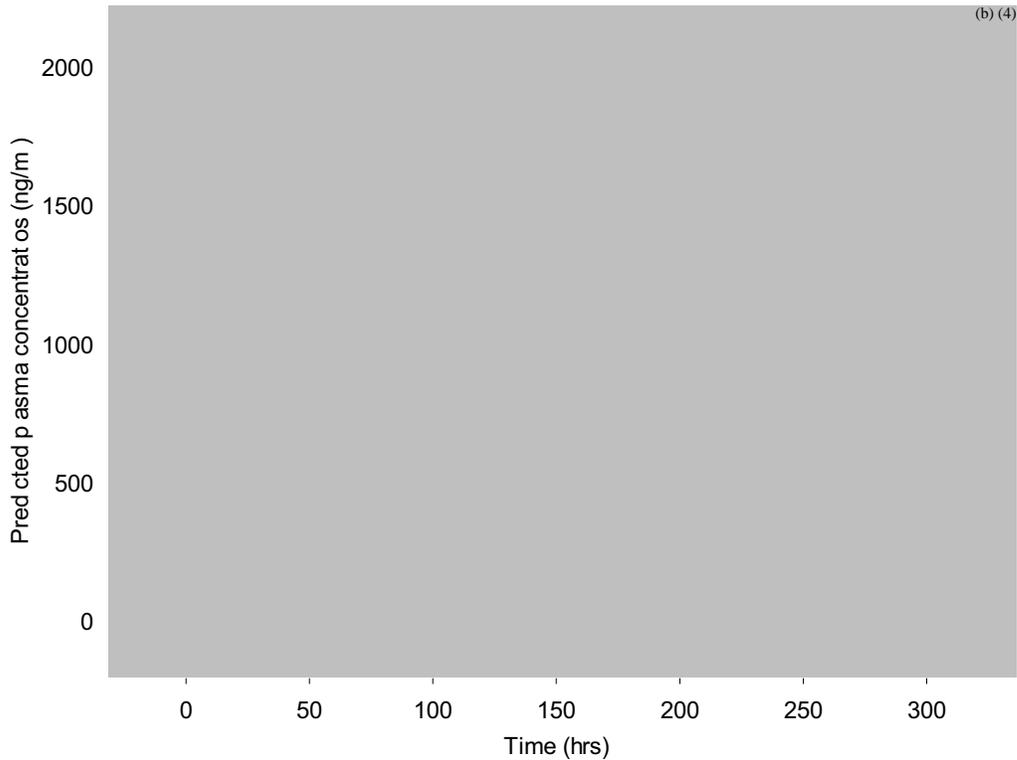


Figure 9. Predicted mean concentration-time profiles for the target formulation and target formulation (b) (4) variation in dissolution profiles (generated using WinNonLin IVIVC Toolkit based on sponsor’s provided data).

Reviewer’s Conclusion

The absolute % difference in predicted AUC and Cmax values corresponding to the high (b) (4) and low (b) (4) proposed dissolution specification with respect to the target specification was lower than (b) (4). Therefore, sponsor’s proposed dissolution specifications for Nevirapine ER Tablets are acceptable as follows:

Table 8. Proposed dissolution specifications for Nevirapine ER Tablets, 400 mg

	<i>Mean in-vitro Profile</i>	<i>Proposed Specification (mean (b) (4) variation)</i>
		% Dissolution
<i>Hours</i>	<i>Clinical Lots (%) Dissolution</i>	
2	14	No more than (b) (4)
8	54	(b) (4)
20	97	NLT (b) (4)

Alcohol Interaction Study

The influence of an alcoholic medium containing 4%, 20%, and 40% ethanol on the in vitro dissolution behavior of Nevirapine ER tablets was investigated. The dissolution conditions were identical to those proposed for routine quality control testing of the drug. There were no signs of an uncontrolled drug release from the formulation of nevirapine ER tablets when dissolved in 4, 20 or 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol. Representative dissolution profiles for the 400 mg tablets is provided in Figure 10.

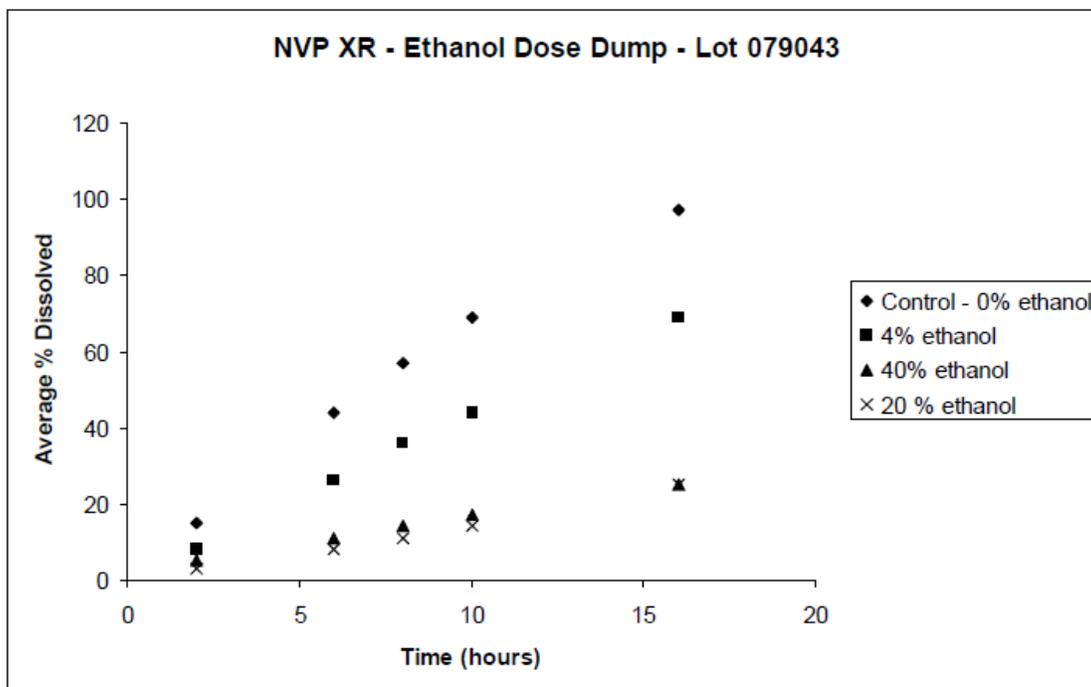


Figure 10. Mean Dissolution Profiles (n=6) of 400 mg Nevirapine Extended-Release Tablets Dissolved in the QC Dissolution Media and in 4, 20 and 40% Alcoholic Medium at 75 rpm USP Apparatus 1 (basket).

It was noted, however, that the provided information on the in vitro alcohol interaction study for Nevirapine ER tablets was obtained using only the proposed QC dissolution method. Therefore, in order to rule out a possible dose-dumping (DD) effect in the presence of alcohol, the Agency sent the following information to the sponsor on September 24, 2010:

1. We recommend that you conduct a drug-alcohol interaction study with your ER product using 0.1 N HCl. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 4 %, 10 %, 20 %, and 40 %. Please also include the following information as part of your report:
 - f2 values to assess the similarity (or lack thereof) in the dissolution profiles.
 - Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hour.

The following information was received from the sponsor on October 4, 2010:

“Concerning the potential for dose dumping in the presence of alcohol and acidic pH, we would like to call FDA’s attention to the submitted Pharmaceutical Development report (Section 3.2.P.2, document U10-3066-01, pages 28 and 29.) As seen in Figure 9 on page 28, in the presence of 0.1N HCl, there is a significant reduction in the extent and rate of release for nevirapine extended-release (ER) tablets, 400 mg. As shown in Figure 10, alcohol added to the proposed dissolution medium (pH 6.8 phosphate buffer with SDS) produces a reduction (not an increase) in drug release rate.

Based on these data, BI did not explore the effect of alcohol on the release profile for the drug product in an acidic medium. Since neither alcohol nor acidic conditions produced dose dumping, we have no expectation that combined alcohol and acid would produce dose dumping. We would respectfully ask that the Division consider whether such studies are needed. If the Division continues to feel such data are required, BI would like to discuss the experimental design (e.g., the concentration(s) of alcohol to be evaluated) via a telecon before performing experiments”

In response to the comments received on Oct 4, 2010 the following comments were conveyed to the sponsor:

1. You have indicated under 32s1 (6654-s130ca0201) that the solubility of nevirapine is strongly pH dependent with increased solubility at acidic pH (at pH 8.0, 0.078 mg/mL; water, 0.092 mg/mL; and pH 1.5, 1.896 mg/mL). We think that the information you provided on Figure 9 on page 28, in the presence of 0.1N HCl, (reduction in the extent and rate of release for nevirapine extended-release (ER) tablets, 400 mg) compared to that at higher pH is misleading due to (b) (4). Therefore, we strongly advise you to conduct an additional drug-alcohol interaction study in 0.1 N HCl with the following alcohol concentrations; 0 %, 4 %, 10 %, 20 %, and 40 % as the dissolution media. Dissolution testing should be conducted using the same apparatus and paddle speed as the QC method. Dissolution data should be generated from 12 dosage units (n 12) at multiple time points to obtain a complete dissolution profile. Please include the following information as part of your study report:
 - The comparison dissolution profile data to determine if the modified release characteristics are maintained, especially in the first 2 hours.
 - The similarity f2 values to assess the similarity (or lack thereof) in the dissolution profiles.

The following response to the comments conveyed above was on Oct 29, 2010:

“BI has conducted an additional drug-alcohol interaction study in 0.1N HCl with the requested alcohol concentrations as the dissolution media. No dose dumping occurred for any of the alcohol concentrations tested; *in vitro* profiles were similar when compared to 0.1N HCl alone using f2 similarity factor calculations”.

Reviewer’s Comments

Figure 11 and Table 9 support the sponsor’s claim about the lack of dose-dumping in the presence of alcohol when tested using the acidic medium.

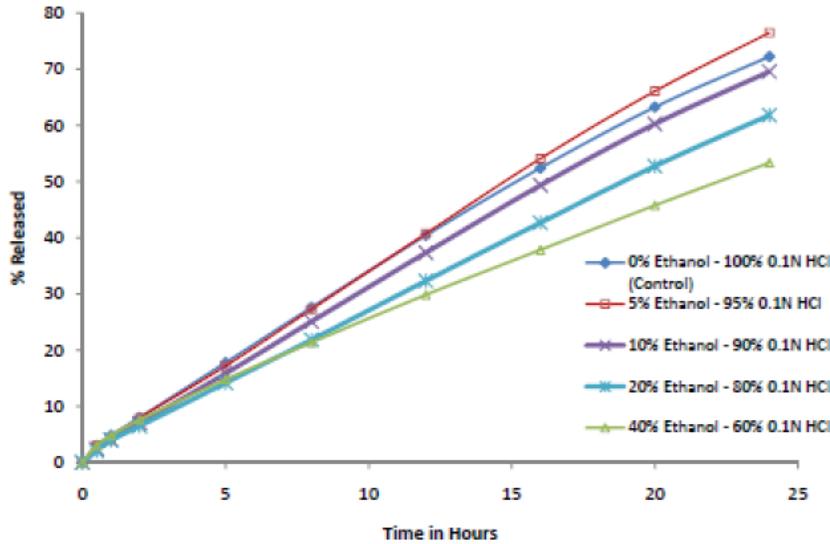


Figure 11. Dissolution profiles for 400 mg nevirapine extended release tablets using dissolution media of varying ethanol content in the presence of 0.1N HCl.

Table 9. Calculated similarity factor (f2) values for *in vitro* dissolution results as a function of dissolution media ethanol concentration combination.

Reference Medium	Test Medium	Similarity Factor f2*
0 % Ethanol/100% 0.1N HCL	5 % Ethanol/95 % 0.1N HCl	83.9
0 % Ethanol/100% 0.1N HCL	10 % Ethanol/90 % 0.1N HCl	83.1
0 % Ethanol/100% 0.1N HCL	20 % Ethanol/80 % 0.1N HCl	61.7
0 % Ethanol/100% 0.1N HCL	40 % Ethanol/60 % 0.1N HCl	51.8

Reviewer’s Conclusion

There were no signs of an uncontrolled drug release from the formulation of nevirapine ER tablets when dissolved in 4, 20 or 40% ethanol tested using either the QC medium or 0.1 N HCl. On the contrary, the release profiles became slower in the presence of alcohol.

Effect of Drug Substance Particle Size on Dissolution

(b) (4)

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/s/

SANDRA SUAREZ
02/25/2011

PATRICK J MARROUM
02/25/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	201152	Brand Name	VIRAMUNE XR
OCP Division (I, II, III, IV, V)	IV	Generic Name	Nevirapine
Medical Division	DAVP	Drug Class	Nonnucleoside reverse transcriptase (NNRTI) inhibitor
OCP Reviewer	Vikram Arya, Ph.D.	Indication(s)	Treatment of HIV-1 infection
OCP Team Leader	Sarah Robertson, Pharm.D.	Dosage Form	400 mg XR tablets
Pharmacometrics Reviewer	TBD	Dosing Regimen	<p><i>Patients Initiating Therapy with VIRAMUNE XR:</i></p> <p>One 200 mg VIRAMUNE IR tablet once-daily for 14 days (lead in period) followed by one 400 mg VIRAMUNE XR tablet once-daily.</p> <p><i>Patients switching from VIRAMUNE IR regimen to VIRAMUNE XR regimen:</i></p> <p>One 400 mg VIRAMUNE XR tablet once-daily without the 14-day lead-in period.</p>
Date of Submission	06/03/2010	Route of Administration	Oral
Estimated Due Date of OCP Review	02/03/2011	Sponsor	Boehringer Ingelheim
Medical Division Due Date	02/15/2011	Priority Classification	Standard
PDUFA Due Date	04/03/2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	N/A			
Mass balance:	N/A			
Isozyme characterization:	N/A			
Blood/plasma ratio:	N/A			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Plasma protein binding:	N/A			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	N/A			
multiple dose:	N/A			
Patients-				
single dose:	N/A			
multiple dose:	N/A			
Dose proportionality -				
fasting / non fasting single dose:	N/A			
fasting / non fasting multiple dose:	N/A			
Drug-drug interaction studies -				
In vivo effects on primary drug:	N/A			
In vivo effects of primary drug:	N/A			
In vitro:	N/A			
Subpopulation studies -				
ethnicity:	N/A			
gender:	N/A			
pediatrics:	N/A			
geriatrics:	N/A			
renal impairment:	N/A			
hepatic impairment:	N/A			
PD -				
Phase 2:	N/A			
Phase 3:	N/A			
PK/PD -				
Phase 1 and/or 2, proof of concept:	N/A			
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics	N/A			
Absolute bioavailability	N/A			
Relative bioavailability -				
solution as reference:	N/A			
alternate formulation as reference:	X	3		
Bioequivalence studies -				
traditional design; single / multi dose:	N/A			
replicate design; single / multi dose:	N/A			
Food-drug interaction studies	N/A			
Bio-waiver request based on BCS	N/A			
BCS class	N/A			
Dissolution study to evaluate alcohol induced dose-dumping	N/A			
III. Other CPB Studies				
Genotype/phenotype studies	N/A			
Chronopharmacokinetics	N/A			
Pediatric development plan	X			
Literature References	N/A			
Total Number of Studies		5		

On **initial** review of the NDA/BLA application for filing:

	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	
2	Has the applicant provided metabolism and drug-drug interaction information?			N/A	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			N/A	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			N/A	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			N/A	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			N/A	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			N/A	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

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

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

NOT APPLICABLE

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

NO FILING ISSUES IDENTIFIED

VIKRAM ARYA, PH.D.	08/04/2010
Reviewing Clinical Pharmacologist	Date
SARAH ROBERTSON, PHARM.D.	08/04/2010
Team Leader/Supervisor	Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-201152

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

Nevirapine Extended Release
Tablets

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/s/

VIKRAM ARYA
08/04/2010

SARAH M ROBERTSON
08/04/2010

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Quality Assessment			
Application No.:	NDA 201-152 (000)	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DAP		
Sponsor:	Boehringer Ingelheim	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Viramune XR	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Nevirapine Extended Release Tablets, 400 mg	Date Assigned:	Jun 16, 2010
Indication:	In combination with other antiretroviral agents for the treatment of HIV-1 infection	Date of Review:	Jun 29, 2010
Formulation/strengths	Extended Release tablets, 400 mg		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
June 3, 2010	June 3, 2010	June 16, 2010	April 3, 2011
Type of Submission:	Original NDA		
Type of Consult:	FILING REVIEW IVIVC model/Dissolution method and specifications/in vitro alcohol interaction study		
REVIEW SUMMARY:			
<p>Viramune[®] (Nevirapine) 200 mg immediate release tablets were approved by the Agency on June 21, 1996 under NDA 20-636. It is indicated for the combination antiretroviral treatment of HIV-1 infection. The recommended dose for Viramune is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents.</p> <p>The sponsor has developed a new formulation for Nevirapine consisting of an extended release tablet for the once daily treatment of HIV-1 infection. The proposed regimen is 400 mg QD. The clinical development program for this new drug formulation for the proposed indication included 3 Phase I studies and 2 Phase III studies. The results of one clinical pharmacology study was utilized for the construction of a Level A in vivo in vitro correlation (IVIVC) for Nevirapine ER, 400 mg tablets.</p> <p>The Level A IVIVC was developed using data from 3 formulations (Nevirapine ER KCR 25%, 30% and 40%) which were manufactured so as to exhibit different release rates as demonstrated by in vitro release tests using USP apparatus type I (40 mesh baskets). The basket rotational speed was kept at 75 rpm. Tablet dissolution was carried out in 900 mL of media (0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate). Data from oral administration of Nevirapine ER KCR 20% Formulation was used to provide an estimate of unit impulse response (UIR). The analyses were performed using the IVIVC ToolkitTM for WinNonlin[®]. Mean data were used to build a correlation as the <i>in vivo</i> study in humans was carried out by parallel design. The procedure of developing an IVIVC followed of a two stage approach (deconvolution followed by convolution. The IVIVC model was internally validated using data utilized in the construction of the model.</p> <p>Under the model assumptions, % error and the MAPPE for the C_{max} and AUC_t values met the internal predictability criteria. However, no external validation information was included. Successful external predictability is needed for full application of the IVIVC since only two of the three formulations used in</p>			

the development of the IVIVC met the criteria of at least (b) (4) difference in *in vitro* release rate and systemic exposure. The sponsor used nevirapine ER KCR 20% as the UIR based on the previous Agency's feedback. It is noted that the UIR formulation has very similar *in vitro* and *in vivo* performance to one of the formulations used in the construction of the IVIVC (Nevirapine ER KCR 25%), which was also (b) (4). This restricts the use of the IVIVC on setting the upper bound specifications for dissolution.

The dissolution method and specifications being proposed by the sponsor for Nevirapine ER Tablets based on the *in vitro* performance of clinical batches, stability batches and IVIVC model are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance criteria
Nevirapine	ER Tablets	USP Basket	75	0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium lauryl sulfate, 900 mL	Time % Label Claim Dissolved 2 hours :Not more than (b) (4) 8 hours: (b) (4) 20 hours: Not less than (b) (4)

On June 17, 2008¹, the Agency approved the proposed IVIVC. Therefore, this review will be focused on the acceptability of the dissolution method, specifications, and the validation of the analytical method. No information was included on the *in vitro* effect of alcohol on dissolution. The sponsor is requested to provide this information.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 201152 (000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter:

- *Submit the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values) for Nevirapine ER Tablets 400 mg.*
- *Submit Complete dissolution profile data (raw data and mean values) for the *in vitro* effect of alcohol on the dissolution profile of Nevirapine ER Tablets or indicate where is this information located in the submission received June 3, 2010.*
- *It is noted that only two formulations used in the construction of the IVIVC meet the requirements of being at least (b) (4) difference in terms of the *in vitro* and *in vivo* performance. Dissolution profiles comparison of K25 vs K30 and K30 vs. K40 generated *f*₂ values higher than 50 (53 and 59, respectively). Therefore, you need to conduct external predictability of the model for full application of the IVIVC. Otherwise, the application of the IVIVC is limited to Category 2a applications (refer to Guidance for Industry -Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlation).*

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

c.c. JDavid, ADorantes, SMiller

¹ ONDQA review entered in DARRTS by Dr. Selen on 07/09/2008.

INTRODUCTION

Viramune[®] (Nevirapine) 200 mg immediate release tablets were approved by the Agency on June 21, 1996 under NDA 20-636. It is indicated for the combination antiretroviral treatment of HIV-1 infection. The recommended dose for Viramune is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents.

The sponsor has developed a new formulation for Nevirapine consisting of an extended release tablet for the once daily treatment of HIV-1 infection. The proposed regimen is 400 mg QD. The sponsor believes that this new formulation presents lower maximum plasma concentrations (Cmax) and lower exposures (AUC) while maintaining a Cmin at 3 µg/mL needed for efficacy. The clinical development program for this new drug formulation for the proposed indication included 3 Phase I studies and 2 Phase III studies. An in vitro alcohol interaction study is also included. The results of one clinical pharmacology study was utilized for the construction of a two Level A in vivo in vitro correlation (IVIVC), one for the 400 mg and one for the 300 mg strengths. This review will be focused on the acceptability of the IVIVC model, dissolution method and specifications, and in vitro alcohol-drug interaction study.

CHEMISTRY

Nevirapine extended-release tablets, 400 mg are yellow, oval, biconvex tablets. The tablets are debossed with product identification “V04” on one side and the BI tower logo on the other side. The qualitative and quantitative compositions of nevirapine extended-release tablets, 400 mg are shown in Table 1.

Table 1. Qualitative and quantitative composition of nevirapine extended-release tablets, 400 mg

Name of Ingredient	mg per tablet	Function	Reference to Standards
Nevirapine Anhydrous	400.00 mg	Drug Substance	Company Standard
Lactose Monohydrate	(b) (4)	(b) (4)	NF/Ph. Eur.
Hypromellose (b) (4)			USP/Ph. Eur.
Iron Oxide (b) (4)			(b) (4)
Magnesium Stearate			NF/Ph. Eur.
(b) (4)			USP/Ph. Eur.
Total Weight			1094 mg*

(b) (4)

Dissolution Method

The dissolution method and specifications being proposed by the sponsor for Nevirapine ER tables is based on the in vitro performance of clinical batches, stability batches and IVIVC model are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Memantine HCl	ER Capsule	I (Basket)	100	pH 1.2 Buffer, Simulated Gastric TS (without pepsin)	900, 37 °C ± 0.5 °C	1 hour: ≤ (b) (4) 4 hours: (b) (4) 8 hours: (b) (4) 12 hours: ≥ (b) (4)

It is noted that the proposed method and specifications are the same as that used in the construction of the IVIVC for Nevirapine ER Tablets. The proposed method and specifications will be a review issue.



Figure 1. Composite plot of all data used in the justification of the dissolution acceptance criteria for nevirapine extended release tablets, 400 mg. L1 acceptance criteria at the 3 designated sample points are indicated by the horizontal reference lines.

IVIVC Model

The IVIVC model has been already reviewed¹. The following recommendation was submitted to the sponsor on June 17, 2008 “The Sponsor has developed a Level A IVIVC for the 400-mg strength nevirapine extended release tablet formulation. Based on in vitro dissolution data, the developed model, within the range explored, is suitable to provide reliable/robust predictions of nevirapine *in vivo* absorption profiles from the extended

release tablets. Following a favorable clinical outcome, this model can be utilized for further regulatory assessments”

Reviewer’s Comments

It is noted however, that the formulations used in the construction of the IVIVC do not meet the requirements of being at least (b) (4) difference in terms of the *in vitro* and *in vivo* performance (see Figures 1-3). Dissolution profiles comparison of K25 vs K30 and K30 vs. K40 generated f_2 values higher than 50 (53 and 59, respectively). Figure 3 shows that formulations 400-K25 and 400-K30 have very similar absorption profile. Therefore, successful external predictability should had been provided for full application of the IVIVC since only two of the three formulations used in the development of the IVIVC met the criteria of at least (b) (4) difference in *in vitro* release rate and systemic exposure.

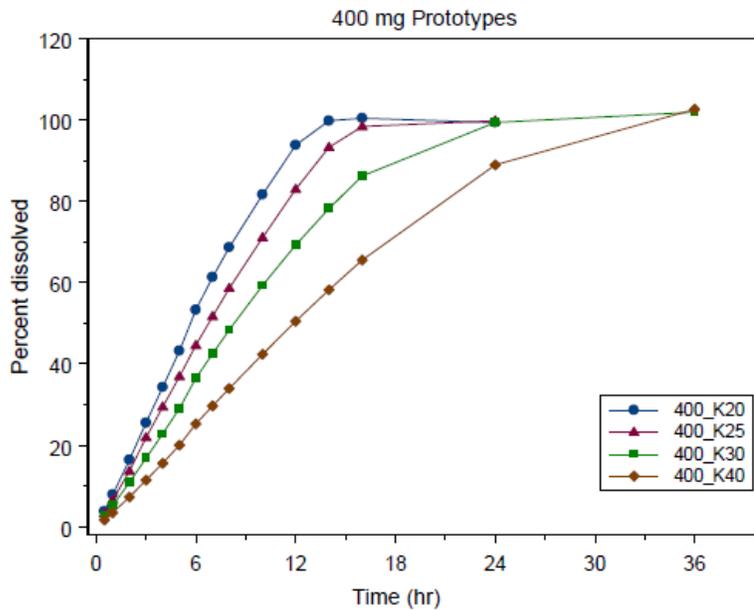


Figure 2. Mean *in vitro* dissolution profiles of nevirapine from 400 mg nevirapine extended release formulations.

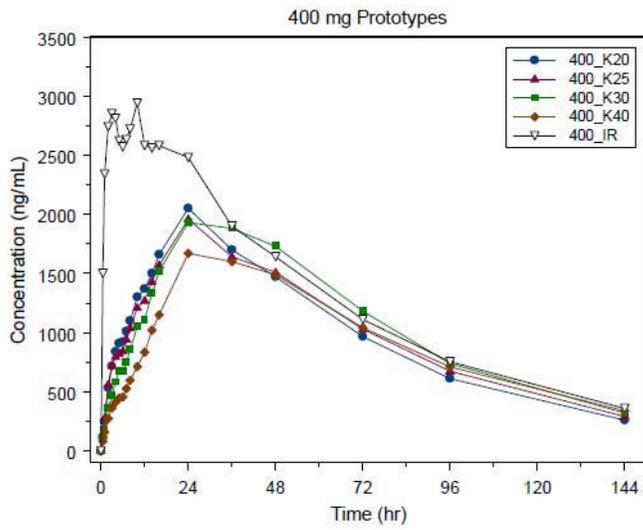


Figure 3. Mean *in vivo* concentration time profiles (0-144 h) of nevirapine following single oral administration of 400 mg nevirapine extended release formulations to healthy volunteers.

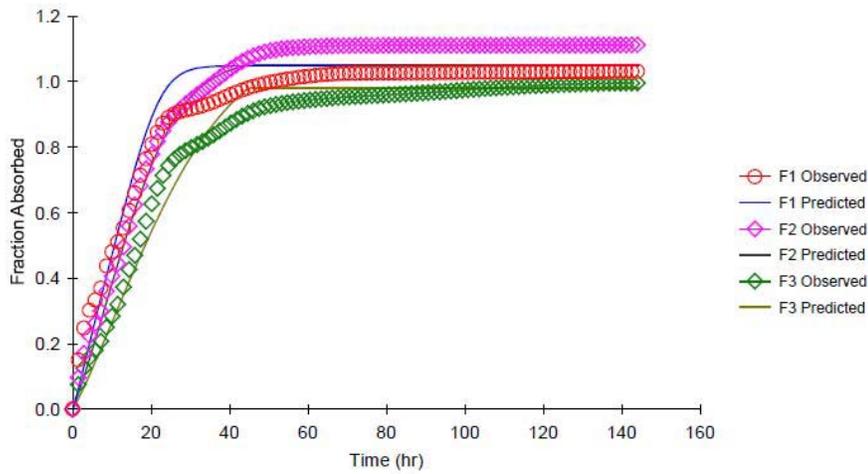


Figure 4. Predicted and observed Nevirapine fraction absorbed following single oral administration of 400 mg nevirapine extended release formulations to healthy volunteers.

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

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/s/

SANDRA SUAREZ
07/14/2010

PATRICK J MARROUM
07/15/2010