



## Clinical trial results:

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

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

EudraCT number	2008-005855-61
Trial protocol	DE Outside EU/EEA
Global end of trial date	10 September 2012

## Results information

Result version number	v2 (current)
This version publication date	02 July 2016
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT-Results

## Trial information

### Trial identification

Sponsor protocol code	1100.1518
-----------------------	-----------

### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00905489
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a>
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a>

Notes:

## Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000391-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	Yes

1901/2006 apply to this trial?
--------------------------------

Notes:

---

### Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2012
Was the trial ended prematurely?	No

Notes:

---

### General information about the trial

Main objective of the trial:

To establish pharmacokinetic (PK) parameters at steady-state of once-daily (QD) Viramune extended release (XR) in children 3-<18 years of age (previously reported) and to evaluate the safety and efficacy profile in children who completed the PK phase and continued Viramune XR in the optional extension phase (OEP).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be randomised to trial treatment. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy:

Other ARVs were continued as chosen by the investigator.

Evidence for comparator:

N/A

Actual start date of recruitment	04 June 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

---

### Population of trial subjects

#### Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Botswana: 64
Country: Number of subjects enrolled	Germany: 12
Worldwide total number of subjects	91
EEA total number of subjects	12

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	56
Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Multicenter study with one treatment group and no randomization process. Overall, 90 pediatric patients were enrolled. Five patients were not entered and 85 patients entered the study. Patients were stratified to the following three age groups: (26 in the 3 -<6 year age group, 26 in the 6 -< 12 year age group and 33 in the 12 -< 18 year age group).

### Pre-assignment

#### Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

### Period 1

Period 1 title	Pharmaco-kinetic (PK) Phase by age
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	3-<6 yr

#### Arm description:

3-<6 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).

Arm type	Treatment sequence
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

Investigational medicinal product name	Viramune ®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

#### Dosage and administration details:

Oral administration of Viramune ® 200 mg tablets or 50mg/5ml oral suspension. Dose depending on body surface or body weight:

Body Surface Area (BSA): 150mg/m<sup>2</sup> twice a day (BID) OR Body Weight (BW): 4 or 7 mg/kg BW BID depending on patient age (7 mg/kg BID if age is 3 to 8 years and 4 mg/kg BID if age is > 8 years)

<b>Arm title</b>	6-<12 yr
------------------	----------

#### Arm description:

6-<12 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).

Arm type	Treatment sequence
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

Investigational medicinal product name	Viramune ®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Viramune ® 200 mg tablets or 50mg/5ml oral suspension. Dose depending on body surface or body weight:

Body Surface Area (BSA): 150mg/m<sup>2</sup> twice a day (BID) OR Body Weight (BW): 4 or 7 mg/kg BW BID depending on patient age (7 mg/kg BID if age is 3 to 8 years and 4 mg/kg BID if age is > 8 years)

<b>Arm title</b>	12-<18 yr
------------------	-----------

Arm description:

12-<18 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).

Arm type	Treatment sequence
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

Investigational medicinal product name	Viramune ®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Viramune ® 200 mg tablets or 50mg/5ml oral suspension. Dose depending on body surface or body weight:

Body Surface Area (BSA): 150mg/m<sup>2</sup> twice a day (BID) OR Body Weight (BW): 4 or 7 mg/kg BW BID depending on patient age (7 mg/kg BID if age is 3 to 8 years and 4 mg/kg BID if age is > 8 years)

<b>Number of subjects in period 1</b> <sup>[1]</sup>	3-<6 yr	6-<12 yr	12-<18 yr
Started	26	26	33
Completed	25	24	31
Not completed	1	2	2
Other reason not defined above	1	1	1
Protocol deviation	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

## Period 2

Period 2 title	Optional Extension Phase (OEP) by age
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	3-<6 yr

Arm description:

3-<6 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.

Arm type	Experimental
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

<b>Arm title</b>	6-<12 yr
------------------	----------

Arm description:

6-<12 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.

Arm type	Experimental
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

<b>Arm title</b>	12-<18 yr
------------------	-----------

Arm description:

12-<18 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.

Arm type	Experimental
Investigational medicinal product name	Nevirapine XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration of various doses: 200 mg (100mg x 2 tablets), 300 mg (100mg x 3 tablets), 400 mg (1 tablet) of Nevirapine extended release (XR) once daily.

<b>Number of subjects in period 2<sup>[2]</sup></b>	3-<6 yr	6-<12 yr	12-<18 yr
Started	12	16	12
Completed	11	16	12
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Extension Phase (OEP) includes only subjects who chose to continue treatment with nevirapine XR after completing the PK phase.

## Baseline characteristics

### Reporting groups

Reporting group title	Pharmaco-kinetic (PK) Phase by age
-----------------------	------------------------------------

Reporting group description: -

Reporting group values	Pharmaco-kinetic (PK) Phase by age	Total	
Number of subjects	85	85	
Age Categorical Units: participants			
Age continuous			
Full analysis set (FAS): All patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.			
Units: years arithmetic mean standard deviation	9.3 ± 4.6	-	
Gender, Male/Female Units: participants			
Female	47	47	
Male	38	38	



## End points

### End points reporting groups

Reporting group title	3-<6 yr
Reporting group description: 3-<6 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).	
Reporting group title	6-<12 yr
Reporting group description: 6-<12 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).	
Reporting group title	12-<18 yr
Reporting group description: 12-<18 years-old subjects initially receive nevirapine immediate release (IR) and then they were switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dose of 200mg, 300mg or 400mg. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).	
Reporting group title	3-<6 yr
Reporting group description: 3-<6 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.	
Reporting group title	6-<12 yr
Reporting group description: 6-<12 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.	
Reporting group title	12-<18 yr
Reporting group description: 12-<18 years-old subjects who chose to continue treatment with nevirapine XR after completing the PK phase.	
Subject analysis set title	NVP XR
Subject analysis set type	Full analysis
Subject analysis set description: Nevirapine XR (extended release)	
Subject analysis set title	NVP IR
Subject analysis set type	Full analysis
Subject analysis set description: Nevirapine IR (immediate release)	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All patients initially receive nevirapine immediate release (IR) and then all patients are switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dosing of 200 mg, 300 mg or 400 mg QD. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).	

### Primary: Trough Cpre,N.

End point title	Trough Cpre,N.
End point description: Trough Nevirapine concentration immediately prior to the next scheduled dose. Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.	

The measure of dispersion presented is the coefficient of variation (%) rather than the geometric coefficient of variation.

PK analysis set (PKS): This patient set includes all patients in the Full Analysis Set (FAS) set that have no protocol violations excluding them from PK analyses.

End point type	Primary
End point timeframe:	
Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR	

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74 <sup>[1]</sup>	78 <sup>[2]</sup>		
Units: (ng/mL/mg)				
geometric mean (geometric coefficient of variation)	15.47 (± 64.34)	16.66 (± 75.03)		

Notes:

[1] - PKS

[2] - PKS

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
----------------------------	------------------------

Statistical analysis description:

Adjusted geometric means were estimated from the mixed model for intra-individual comparison.

The actual number of subjects analyzed is 78. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (152) does not reflect the actual number.

Ratio calculated as NVP XR: NVP IR.

Comparison groups	NVP XR v NVP IR
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.008
Method	Mixed models analysis
Parameter estimate	Ratio [NVP XR: NVP IR]
Point estimate	91.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.47
upper limit	99.64
Variability estimate	Standard error of the mean
Dispersion value	1.05

Notes:

[3] - No formal hypothesis testing.

---

**Secondary: AUCt,ss**

---

End point title	AUCt,ss
-----------------	---------

End point description:

Area under the concentration-time curve of the Nevirapine (NVP) in plasma at steady state over the time dosing interval t.

All patients received nevirapine IR for 10 days prior to collection of 12-hour Area Under the Curve (AUC) data. Then, all patients were switched to nevirapine XR for 9 days prior to collection of 24-hour AUC data. The treatments of IR and XR are summarized separately using geometric means and geometric coefficients of variation.

For NVP IR AUC measured over hours: 0,1,2,3,4,8 and 12,

For NVP XR AUC measured over hours: 0,1,2,3,4,8,10,12 and 24.

Intensive PK analysis set (IPK): This patient set includes all patients in the PK set that underwent intensive PK sampling.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR

---

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[4]</sup>	49 <sup>[5]</sup>		
Units: ng*h/ml				
geometric mean (geometric coefficient of variation)				
200mg NVP XR QD (175-249 mg IR/day), n=23/22	99300 (± 37.7)	57900 (± 45.7)		
300mg NVP XR QD (250-349 mg IR/day), n=11/12	144000 (± 50.1)	58100 (± 35)		
400mg NVP XR QD (≥350 mg IR/day), n=11/15	108000 (± 60.7)	73400 (± 39.8)		

Notes:

[4] - Intensive PK analysis set (IPK)

[5] - Intensive PK analysis set (IPK)

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Cmin,ss (for IR and XR formulations by nevirapine XR dose group)**

---

End point title	Cmin,ss (for IR and XR formulations by nevirapine XR dose group)
-----------------	--

End point description:

Minimum measured concentration of the Nevirapine in plasma at steady state over the time dosing interval  $\tau$  by nevirapine XR dose group patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 21.

Intensive PK analysis set (IPK): This patient set includes all patients in the PK set that underwent intensive PK sampling.

End point type	Secondary
End point timeframe:	
Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR	

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[6]</sup>	49 <sup>[7]</sup>		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	3090 (± 37.9)	3280 (± 57.6)		
300 mg XR QD (250-349 mg IR/day), n=11,12	4160 (± 62.6)	3620 (± 34.7)		
400 mg XR QD (≥350 mg IR/day), n=11,15	3410 (± 63)	4960 (± 39.1)		

Notes:

[6] - IPK

[7] - IPK

## Statistical analyses

No statistical analyses for this end point

## Secondary: C<sub>max,ss</sub> (for IR and XR formulations by nevirapine XR dose group)

End point title	C <sub>max,ss</sub> (for IR and XR formulations by nevirapine XR dose group)
End point description:	
Maximum measured concentration of the Nevirapine in plasma at steady state over the time dosing interval τ. Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.	
End point type	Secondary
End point timeframe:	
Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR	

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[8]</sup>	49 <sup>[9]</sup>		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	5350 (± 43.1)	6850 (± 52.6)		
300 mg XR QD (250-349 mg IR/day), n=11,12	7970 (± 53.5)	6580 (± 31.4)		

400 mg XR QD ( $\geq 350$ mg IR/day), n=11,15	5890 ( $\pm 50.5$ )	7790 ( $\pm 43.2$ )		
--	---------------------	---------------------	--	--

Notes:

[8] - IPK

[9] - IPK

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ratio C<sub>max,ss</sub>/C<sub>min,ss</sub>

End point title	Ratio C <sub>max,ss</sub> /C <sub>min,ss</sub>
-----------------	--

End point description:

Ratio of (maximum measured concentration of the Nevirapine in plasma at steady state over the time dosing interval  $\tau$ )/(minimum measured concentration of the analyte in plasma at steady state over the time dosing interval  $\tau$ ). Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR.

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[10]</sup>	49 <sup>[11]</sup>		
Units: Ratio				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	1.73 ( $\pm 23.7$ )	2.09 ( $\pm 32.3$ )		
300 mg XR QD (250-349 mg IR/day), n=11,12	1.91 ( $\pm 39.4$ )	1.82 ( $\pm 17.8$ )		
400 mg XR QD ( $\geq 350$ mg IR/day), n=11,15	1.73 ( $\pm 21.8$ )	1.57 ( $\pm 21.1$ )		

Notes:

[10] - IPK

[11] - IPK

## Statistical analyses

No statistical analyses for this end point

### Secondary: %PTF

End point title	%PTF
-----------------	------

End point description:

Percentage peak-trough Nevirapine fluctuation, % fluctuation (degree of peak to trough fluctuation). Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[12]</sup>	49 <sup>[13]</sup>		
Units: percentage fluctuation				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	49.7 (± 47.3)	67.9 (± 49.8)		
300 mg XR QD (250-349 mg IR/day), n=11,12	54.6 (± 61.1)	59.1 (± 29.4)		
400 mg XR QD (≥350 mg IR/day), n=11,15	51 (± 47.6)	41.5 (± 55.7)		

Notes:

[12] - IPK

[13] - IPK

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax,ss

End point title	Tmax,ss
-----------------	---------

End point description:

Time from dosing to the maximum concentration of the Nevirapine in plasma at steady state over the time dosing interval  $\tau$  Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.

The measure of dispersion presented is the coefficient of variation (%) rather than the standard deviation.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[14]</sup>	49 <sup>[15]</sup>		
Units: hours				
arithmetic mean (standard deviation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	6.34 (± 104)	2.46 (± 57.9)		
300 mg XR QD (250-349 mg IR/day), n=11,12	7.28 (± 121)	2.49 (± 50.4)		

400 mg XR QD ( $\geq 350$ mg IR/day), n=11,15	5.73 ( $\pm 129$ )	4.41 ( $\pm 94.2$ )		
--	--------------------	---------------------	--	--

Notes:

[14] - IPK

[15] - IPK

## Statistical analyses

No statistical analyses for this end point

## Secondary: CL/F,ss

End point title	CL/F,ss
-----------------	---------

End point description:

Apparent clearance of the Nevirapine in the plasma after extravascular administration at steady-state Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[16]</sup>	49 <sup>[17]</sup>		
Units: mL/h				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	2010 ( $\pm 37.7$ )	1780 ( $\pm 44.3$ )		
300 mg XR QD (250-349 mg IR/day), n=11,12	2080 ( $\pm 50.1$ )	2240 ( $\pm 32.9$ )		
400 mg XR QD ( $\geq 350$ mg IR/day), n=11,15	3700 ( $\pm 60.7$ )	2640 ( $\pm 39.3$ )		

Notes:

[16] - IPK

[17] - IPK

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cavg

End point title	Cavg
-----------------	------

End point description:

Average measured concentration of the Nevirapine in plasma at steady state Patients took Nevirapine (NVP) Immediate Release (IR) up to day 10 and had PK measurements taken on Day 11. This was followed by 9 days (from day 12 to day 20) taking NVP Extended Release (XR) with PK measurements taken on Day 22.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 11 prior to the next scheduled dose of Nevirapine IR and day 22 prior to the next scheduled dose of Nevirapine XR

End point values	NVP XR	NVP IR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45 <sup>[18]</sup>	49 <sup>[19]</sup>		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
200 mg XR QD (175-249 mg IR/day), n=23,22	4140 ( $\pm$ 37.7)	4820 ( $\pm$ 45.7)		
300 mg XR QD (250-349 mg IR/day), n=11,12	6010 ( $\pm$ 50.1)	4840 ( $\pm$ 35)		
400 mg XR QD ( $\geq$ 350 mg IR/day), n=11,15	4510 ( $\pm$ 60.7)	6120 ( $\pm$ 39.8)		

Notes:

[18] - IPK

[19] - IPK

## Statistical analyses

No statistical analyses for this end point

## Secondary: Efficacy: Patients maintaining a VL < 50 copies/mL

End point title	Efficacy: Patients maintaining a VL < 50 copies/mL
End point description:	
Patients maintaining a viral load < 50 copies/mL at Day 22.	
Full analysis set (FAS): This analysis set includes patients with available viral load data at day 22	
End point type	Secondary
End point timeframe:	
Day 22	

End point values	3-<6 yr	6-<12 yr	12-<18 yr	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	25 <sup>[20]</sup>	23 <sup>[21]</sup>	31 <sup>[22]</sup>	79 <sup>[23]</sup>
Units: percentage of patients				
number (not applicable)	96	100	100	98.7

Notes:

[20] - FAS

[21] - FAS

[22] - FAS

[23] - FAS

## Statistical analyses



No statistical analyses for this end point

### Secondary: Efficacy: Patients Maintaining a VL < 400 Copies/mL

End point title Efficacy: Patients Maintaining a VL < 400 Copies/mL

End point description:

Patients maintaining a viral load < 400 copies/mL at Day 22.

Full analysis set (FAS) including patients with available viral load data at day 22.

End point type Secondary

End point timeframe:

Day 22

End point values	3-<6 yr	6-<12 yr	12-<18 yr	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	25 <sup>[24]</sup>	23 <sup>[25]</sup>	31 <sup>[26]</sup>	79 <sup>[27]</sup>
Units: percentage of patients				
number (not applicable)	100	100	100	100

Notes:

[24] - FAS

[25] - FAS

[26] - FAS

[27] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in mean CD4+ count (absolute)

End point title Change from baseline in mean CD4+ count (absolute)

End point description:

Change in mean CD4+ count (absolute) from baseline to Day 22 and from baseline to Week 24.

End point type Secondary

End point timeframe:

Baseline, Day 22 and Week 24

End point values	3-<6 yr	6-<12 yr	12-<18 yr	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24 <sup>[28]</sup>	24 <sup>[29]</sup>	31 <sup>[30]</sup>	
Units: cells/mm <sup>3</sup>				
arithmetic mean (standard deviation)				
Day 22	-115.6 (± 320.5)	24.2 (± 184.8)	60.3 (± 171.2)	
Week 24 (n=8; 10; 9)	-214.5 (± 397.5)	-51.2 (± 179.4)	31.1 (± 66.4)	

Notes:

[28] - PKS

[29] - PKS

[30] - PKS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in mean CD4+ count

End point title	Percentage change from baseline in mean CD4+ count
-----------------	--

End point description:

((Day 22 value-Baseline value)/Baseline value)\*100.

((Week 24 value-Baseline value)/Baseline value)\*100.

Optional Extension Phase Treated Set (OEP TS), all patients that complete PK phase and enroll in Extension phase, and had available data at either day 22 or week 24.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline to Day 22 and baseline to Week 24

End point values	3-<6 yr	6-<12 yr	12-<18 yr	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24 <sup>[31]</sup>	24 <sup>[32]</sup>	31 <sup>[33]</sup>	
Units: percentage change				
arithmetic mean (standard deviation)				
Day 22	-2.1 (± 6.7)	0 (± 2.5)	0.5 (± 3.6)	
Week 24 (n=8; 10; 9)	-2.1 (± 4)	-2.1 (± 3.4)	-1 (± 2.9)	

Notes:

[31] - OEP TS

[32] - OEP TS

[33] - OEP TS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Efficacy: Patients maintaining a VL < 50 copies/mL at week 24 of Optional Extension Phase

End point title	Efficacy: Patients maintaining a VL < 50 copies/mL at week 24 of Optional Extension Phase
-----------------	---

End point description:

Patients maintaining a viral load < 50 copies/mL at week 24 (approximately 168 days) of Optional Extension Phase (OEP).

Full analysis set including patients with available viral load data at week 24.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	3-<6 yr	6-<12 yr	12-<18 yr	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8 <sup>[34]</sup>	10 <sup>[35]</sup>	9 <sup>[36]</sup>	27 <sup>[37]</sup>
Units: percentage of patients				
number (not applicable)	100	100	100	100

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

[37] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: Efficacy: Patients Maintaining a VL < 400 Copies/mL in Optional Extension Phase

End point title	Efficacy: Patients Maintaining a VL < 400 Copies/mL in Optional Extension Phase
-----------------	---

End point description:

Patients maintaining a viral load < 400 copies/mL at week 24 of the Optional Extension Phase (OEP).

Full analysis set including patients with available viral load data at week 24

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	3-<6 yr	6-<12 yr	12-<18 yr	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8 <sup>[38]</sup>	10 <sup>[39]</sup>	9 <sup>[40]</sup>	27 <sup>[41]</sup>
Units: percentage of patients				
number (not applicable)	100	100	100	100

Notes:

[38] - FAS

[39] - FAS

[40] - FAS

[41] - FAS

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Efficacy: Patients Maintaining a VL < 50 Copies/mL at Last Available Visit

End point title	Efficacy: Patients Maintaining a VL < 50 Copies/mL at Last Available Visit
-----------------	--

---

End point description:

Patients maintaining a viral load < 50 copies/mL at the last available visit.

Optional Extension Phase Treated Set (OEP TS), all patients that complete PK phase and enroll in Extension phase with VL data available.

---

End point type	Other pre-specified
----------------	---------------------

---

End point timeframe:

Last available visit, up to 155 weeks

---

End point values	3-<6 yr	6-<12 yr	12-<18 yr	Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	12 <sup>[42]</sup>	16 <sup>[43]</sup>	12 <sup>[44]</sup>	40 <sup>[45]</sup>
Units: percentage of patients	100	100	100	100

Notes:

[42] - OEP TS

[43] - OEP TS

[44] - OEP TS

[45] - OEP TS

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 14 days after the last drug administration, up to 157 weeks.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.0
--------------------	------

### Reporting groups

Reporting group title	Total
-----------------------	-------

Reporting group description:

All patients enrolled in study. All patients initially receive nevirapine immediate release (IR) and then all patients are switched to nevirapine extended release (XR) 100mg or 400mg tablets for a once daily dosing of 200 mg, 300 mg or 400 mg QD. After completing the PK phase patients had the option of continuing treatment with nevirapine XR in the Optional Extension Phase (OEP).

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 85 (3.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Coxsackie viral infection			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonia</b>			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 85 (65.88%)		
<b>Nervous system disorders</b>			
Headache			
subjects affected / exposed	14 / 85 (16.47%)		
occurrences (all)	18		
<b>General disorders and administration site conditions</b>			
Pyrexia			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	11		
<b>Eye disorders</b>			
Conjunctivitis			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	13		
<b>Gastrointestinal disorders</b>			
Diarrhoea			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	8		
Vomiting			

subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 12		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	28 / 85 (32.94%) 39		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	20 / 85 (23.53%) 24		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)  Body tinea subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  Respiratory tract infection subjects affected / exposed occurrences (all)  Rhinitis subjects affected / exposed occurrences (all)  Tinea capitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)  Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 85 (5.88%) 9  5 / 85 (5.88%) 5  5 / 85 (5.88%) 12  6 / 85 (7.06%) 8  8 / 85 (9.41%) 12  7 / 85 (8.24%) 12  33 / 85 (38.82%) 46  9 / 85 (10.59%) 12		





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2009	Clarification of the PK analyses including primary and secondary endpoints
08 September 2009	<ol style="list-style-type: none"><li>1. To change the definition of virologic failure</li><li>2. Inclusion of Vital Status for patients who discontinue early after entering the OEP</li><li>3. To increase the number patients assigned to post-dose PK sampling in the 3-&lt;6 years age group</li><li>4. Clarification of the PK analyses including the primary and secondary endpoints</li><li>5. To allow flexibility in the method of calculating the dose of Viamune IR during the run-in phase</li><li>6. To update the dose adjustment methodology of Viamune XR during the OEP</li></ol>

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported