Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Title of trial:	A randomised, double blind, double dummy, parallel group, active controlled trial to evaluate the antiviral efficacy of 400 mg QD neVirapine Extended Release formulation in comparison to 200 mg BID neVirapinE immediate release in combination with Truvada® in antiretroviral therapy naïve HIV-1 infected patients **(VERXVE)**
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter Study, c.f. Appendix 16.1.4
Publication (reference):	P11-06285
Clinical phase:	III
Objectives:	The primary objective of this trial is to evaluate the efficacy and safety of 400 mg QD nevirapine extended release (NVP XR) formulation versus 200 mg BID nevirapine immediate release (NVP IR) in ARV therapy naïve HIV-1 infected patients after 48 weeks of treatment. The objective of this CTR is to evaluate the efficacy and safety of 400 mg QD nevirapine extended release (NVP XR) formulation versus 200 mg BID nevirapine immediate release (NVP IR) in ARV therapy naïve HIV-1 infected patients after 144 weeks of treatment. Safety and efficacy data will also be presented descriptively for the post week 144 open label extension phase of the trial where all patients received open label nevirapine XR.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Methodology:	Eligible patients were stratified by their baseline HIV-1 viral load (defined as the maximum of screening viral load or Day 0 viral load) to ≤100,000 copies/mL or > 100,000 copies/mL strata. Within each stratum, they were randomised to receive 400 mg QD nevirapine XR or 200 mg BID nevirapine IR, after a 14 day lead in period in which all the patients received 200 mg QD nevirapine IR formulation. Background ARV therapy is Truvada® (emtricitabine and tenofovir disoproxil fumarate) QD in both treatment groups. Treatment duration for the primary endpoint was 48 weeks with an extension of up to Week 144. Efficacy, safety, and pharmacokinetic (PK) parameters will be evaluated at each study visit. At the conclusion of 144 weeks of blinded treatment each patient then had the option to enter an open label extension phase of the trial where they would be dosed with open label nevirapine XR and truvada. Patients would have visits every 12 weeks during this open label extension and such visits would continue until the last patient enrolled in the trial completed 144 weeks of blinded treatment. At that point each patient would be brought in for an end of trial visit within 30 days. The purpose of the extension is to allow for the collection of long term safety and efficacy data. In this report cumulative data from the blinded period of the trial up to last patient out at Week 144 is evaluated for efficacy. In addition efficacy data for the open label extension is also descriptively presented. Cumulative data for safety during the total time over the course of the trial that patients were exposed to a certain treatment is also evaluated.
No. of subjects:	
planned:	enrolled: 1250 entered and randomized: 958
actual:	enrolled: 1626 Treatment: Nevirapine XR entered: 505 treated: 505 analyzed (for primary endpoint): Treatment: Nevirapine IR entered: 508 treated: 506 analyzed (for primary endpoint):

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Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Diagnosis and main criteria for inclusion:	Patients meeting the following criteria will be eligible for participation in this study: 1. Signed informed consent in accordance with GCP and local regulatory requirements prior to trial participation 2. HIV-1 infected males or females ≥18 years of age with positive serology (ELISA) confirmed by Western blot 3. No previous antiretroviral treatment 4. Males with CD4+ counts >50-<400 cells/µl or females with CD4+ counts >50-<250 cells/µl 5. Adequate renal function defined as a calculated creatinine clearance (CLCr) greater than or equal to 50 mL/min according to the Cockcroft-Gault formula as follows: Male: (140 – age in years) x (weight in kg) divided by 72 x (serum creatinine in mg/dl) = CLCr (mL/min). Female: (140 – age in years) x (weight in kg) divided by 72 x (serum creatinine in mg/dl) x 0.85 = CLCr (mL/min). 6. Karnofsky score >70 7. An HIV-1 viral load of ≥1,000 copies/mL 8. Willingness to initiate CD4+ cell count-guided chemoprophylaxis to prevent important opportunistic infections as defined in Appendix 10.2 of the protocol. 9. Willingness to abstain from ingesting substances which may alter plasma study drug levels by interaction with the cytochrome P450 system (listed in Appendix 10.3 of the protocol) during the study.
Test product:	Nevirapine extended release (XR)
dose:	400 mg 1 tablet QD from Day 15 to Week 48 (maximum to last patient completing Week 144)
mode of admin.:	Oral
batch no.:	B073000622, B083000134, B083000135 B093000579, B093000913, B093000930 Placebo: B073000397, B083000261, B083000260, B103000232

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Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Reference therapy:	Nevirapine immediate release (IR)
dose:	200 mg 1 tablet BID from Day 15 to Week 48 (maximum to Week 144)
mode of admin.:	Oral
batch no.:	B073000393, B083000256, B08300025, B103000230 Placebo: B073000398, B083000258, B083000259, B103000229
Duration of blinded treatment:	48 weeks minimum to last patient completing Week 144
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint of this study was sustained virologic response at Week 48. A virologic response was defined by two consecutive measurements of VL <50 copies/mL, at least two weeks apart. A sustained virologic response had no virologic rebound or change of ARV therapy through Week 48. The time window of Week 48 was defined as 48±4 weeks from Day 1 (the day a patient starts treatment). A virologic rebound was defined by two consecutive measurements of VL ≥50 copies/mL, at least two weeks apart, after a virologic response. If there was unconfirmed change of VL status (rebound or response) at Week 48, then another measurement at least two weeks later was necessary to confirm whether virologic rebound or response had occurred. Secondary endpoints summarized in this Week 144 CTR include • sustained virologic response at Week 144 using LLOQ = 50 copies/mL • time to loss of virologic response • change from baseline in viral load and CD4+ cell count at Week 144 **Pharmacokinetic parameters:** Trough ($C_{pre,ss,N}$ for all patients)

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Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Safety:	Safety: Safety endpoints included:
	• Adverse events
	• Serious adverse events (including AIDS-defining events)
	• Occurrence of AEs, by severity and by action taken with regard to trial drug
	• Occurrence of discontinuations due to AEs.
	• Occurrence of rashes and hepatic events
	• Change in laboratory test value from baseline
	• Occurrence of elevations in laboratory measurements by DAIDS Grade
	• Time-to-event endpoints
	  o Time to permanent discontinuation of study medication
	  o Time to permanent discontinuation of study medication due to AEs
	  o Time to Grade 3 or 4 ALT/AST abnormalities
	  o Time to Grade 3 or 4 asymptomatic transaminases
	  o Time to clinical hepatic events

Statistical methods:	This study was powered (90%) to demonstrate non-inferiority (NI) of nevirapine XR formulation to nevirapine IR formulation with regard to proportion of sustained virologic response at Week 48 using -10% NI margin. The difference and 95% CI in proportions between two treatment groups were derived using Cochran's statistic with continuity correction for variance calculation. Non-inferiority of XR to IR with regard to efficacy would be established if the lower limit of the CI was greater than -10%. The planned sample size n = 479 per group had at least 90% of power in order to claim non-inferiority with one-sided alpha = 0.025, assuming that the expected difference of proportions between the two treatment groups is 0 and the virologic response proportion in both groups was 65%. All safety parameters (adverse events, changes in laboratory, discontinuation due to adverse events) were analyzed descriptively. Descriptive statistics for pharmacokinetic parameters were calculated.

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Name of active ingredient: Nevirapine		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The efficacy results indicate that nevirapine XR is non-inferior to nevirapine IR with regard to HIV-1 viral load suppression at Week 144 in ARV treatment-naïve HIV-1 positive patients.

Proportion of sustained virologic response at Week 144

Based on the TLOVR algorithm, the sustained virologic response proportion at Week 144 was 58.5% for nevirapine IR and 63.6% for nevirapine XR, with an adjusted difference of 4.8% (95% CI: -1.1%, 10.8%) in favor of nevirapine XR, indicating the non-inferiority of nevirapine XR to nevirapine IR using the -10% non-inferiority margin. The result is robust when the supplemental SNAPSHOT approach was used: adjusted difference was 4.1% (95% CI: -1.8%, 9.9%) favoring nevirapine XR. Subgroup analyses of the primary endpoint suggested that (1) there were no relationships between baseline demographics (age group, gender, race and region) and proportion of sustained virologic response at Week 144; (2) baseline HIV-1 viral load ≤100,000 copies/mL stratum had a higher proportion of sustained virologic response at Week 144 than the >100,000 stratum; there were no relationship between other baseline characteristics (CD4+ cell count, HIV-1 sub-type, CDC class, and lead-in duration) and proportion of sustained virologic response proportion at Week 144.

Other secondary endpoints

No meaningful differences were observed between the two treatment groups with regard to time to loss of virologic response, change in viral load from baseline at Week 144, change in CD4+ cell count from baseline at Week 144, or time to new AIDS or AIDS-related progression event or death.

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Name of finished product: Nevirapine XR		**EudraCT No.:** 2007-003654-29	
Name of active ingredient: Nevirapine		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Efficacy / clinical pharmacology results: (cont'd)

Pharmacokinetic endpoints

Nevirapine XR trough concentrations were 79.58% of nevirapine IR at Week 132, and geometric mean of nevirapine XR trough concentrations of all weeks were 80.98% of nevirapine IR. The relative trough exposure of nevirapine XR to IR was consistent among gender, race, region, and baseline viral load stratum. In spite of lower trough concentration, the nevirapine XR group demonstrated non-inferior efficacy to nevirapine IR group, indicative of adequate trough drug exposure ofnevirapine XR. Pharmacokinetic results suggest that nevirapine XR tablet formulation performed consistently well following once daily oral administration in HIV-1 patients with Truvada as ARV background therapy.

Safety results:

Of 1011 patients who received at least one dose of blinded study medication, 506 patients received 200 mg of nevirapine IR BID and 505 patients received 400 mg of nevirapine XR QD. The nevirapine XR group had 381 (75.4%) patients with greater than 132 weeks of exposure to blinded study drug while the nevirapine IR group had 358 (70.8%) patients with a similar extent of exposure. However around the week 144 time point 328 of the 381 patients receiving blinded NVP XR entered the post week 144 extension and began receiving open label nevirapine XR and truvada. For the blinded nevirapine IR group 315 of the 358 patients entered the open label extension and began receiving open label nevrapine XR and truvada. One patient in the blinded nevirapine IR group who continued in the study after week 144 did not enter the open label extension but rather elected to continue to receive NVP IR. During the open label extension period patients who received IR and XR during the blinded phase of the trial had similar durations of exposure to open label nevirapine XR.

Overall the safety findings for the nevirapine IR and XR groups after the last patient completed week 144 were similar to those reported at earlier points in time in the trial (week 48 and week 96). Adverse event rates were similar for the two groups, but the nevirapine IR group tended to have a higher numbers of patients; 1) with AEs overall 2) with AEs related to study medication 3) with AEs leading to discontinuation of study medication and 4) with DAIDS grade 3 or 4 AEs. The nevirapine XR group had a higher frequency of patients with SAEs. This finding indicates how well tolerated the XR formulation was since the overall extent of exposure of patients receiving nevirapine IR was less than for those receiving

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Name of active ingredient: Nevirapine		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 July 2012	**Trial No. / U No.:** 1100.1486/ U12-3368-01	**Date of trial:** 15 November 2007 to 24 November 2011	**Date of revision:** Not applicable

Safety results:(cont'd)	nevirapine XR due to the 315 IR patients who stopped taking the IR formulation around week 144 and entered the post week 144 extension where they received open label nevirapine XR. There were 16 deaths in the 1100.1486 study from inception to completion (as of the final database lock snapshot on 13 January 2012). Three additional patients died since week 96, one due to acute myocardial infarction, one due to dyspnoea and one due to bone cancer. None of the deaths were related to study medication. No patient died during the open label extension phase of the trial. The three most common SAEs continued to be pneumonia, depression and Kaposi's sarcoma. In conclusion, at the point when the last patient completed week 144 in this trial nevirapine XR was shown to be safe and tolerable. Overall nevirapine XR has a safety profile similar to nevirapine IR, though with fewer AEs. No new safety findings were reported in this final report.
Conclusions:	Over the entire duration of this trial nevirapine XR 400 mg QD has continued to demonstrate non inferiority to nevirapine IR 200 mg BID with regard to viral load suppression, indicative of adequate trough drug exposure of nevirapine XR. Nevirapine XR was demonstrated to be reasonably safe and tolerable over the course of the trial. Nevirapine XR had a safety profile similar to nevirapine IR, though with numerically fewer AEs. No new safety findings were observed in this final report.