Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Nevirapine XR		**EudraCT No.:** 2008-004681-55	
Name of active ingredient: Nevirapine		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 08 JUL 2014	**Trial No. / U No.:** 1100.1526 / U12-3442-01	**Date of trial:** 06 JAN 2009 –29 DEC 2011	**Date of revision** Not applicable.

Title of trial:	An open label, phase IIIb, randomized, parallel group study to assess the efficacy and safety of switching HIV-1 infected patients successfully treated with a Nevirapine IR based regimen to Nevirapine XR 400 mg QD or remaining on Nevirapine IR 200 mg BIDbased regimen
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, cf. Appendix 16.1.4
Publication (reference):	Data from this study have not yet been published
Clinical phase:	IIIb
Objectives:	To assess the efficacy and safety of switching HIV-1 infected patients from Nevirapine IR based regimen to Nevirapine XR based regimen
Methodology:	Open label, randomized, parallel group study. After screening, patients were randomized with a 2:1 allocation ratio to Nevirapine XR 400 mg QD or Nevirapine IR 200 mg BID. Patients remained on their previous background therapy. Treatment duration was 48 weeks with an extension to 144 weeks. The randomization at baseline was stratified by background therapy. After week 48 patients assigned to the nevirapine IR group had the option to switch to a nevirapine XR regimen. Previously two interim clinical trial reports were done ,one after the last patient completed the first 24 weeks of the study (U10-3028-01) and another after the last patient completed the first 48 weeks of the study(U10-3651-02). This final clinical trial report presents results for the entire 144 week duration of the trial.
No. of subjects:	
planned:	entered: 300 (200 Nevirapine XR, 100 Nevirapine IR)

actual:	enrolled: 499 Treatment Nevirapine Extended Release 400 mg QD: entered: 296 treated: 295 analysed (for secondarydpoint):295 Treatment Nevirapine Immediate Release 200 mg BID: entered: 149 treated: 148 analysed (for secondary endpoint): 148 **Post week 48:** 419 patients went on to participate in the study post week 48. Of those, 143 patients had been randomized to nevirapine IR and 276 were randomized to nevirapine XR. Since patients originally randomized to nevirapine IR had the option to switch to nevirapine XR post week 48, 130 of the 143 patients in the nevirapine IR group switched to a nevirapine XR based regimen while the other 13 patients stayed on their nevirapine IR based regimen. All 276 patients randomized to nevirapine XR continued this regimen post week 48.
Diagnosis and main criteria for inclusion:	HIV-1 infected subjects treated with Viramune® based regimen. Subjects that met the following inclusion criteria were eligible: 1. Treated with Viramune® regimen for at least the preceding 18 weeks. 2. Background therapy with 3TC/ABC (Kivexa® in EU; Epzicom™ in US), FTC/TDF (Truvada™) or 3TC/AZT (Combivir®) for at least the preceding 18 weeks. 3. An undetectable HIV-1 viral load in preceding 1-4 months and at screening (Visit 1)
Test product:	Nevirapine Extended Release
dose:	400 mg QD
mode of admin.:	Oral
batch no.:	See Appendix 16.1.6
Reference therapy:	Nevirapine Immediate Release
dose:	200 mg QD

mode of admin.:	Oral
batch no.:	See Appendix 16.1.6
Duration of treatment:	48 Week trial period with an 144 week extension
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the proportion of patients with sustained virologic response (viral load <50 copies mL) through Week 24. A patient was considered as a treatment failure at the earliest time of any one of the following events prior to Week 24: • A virologic failure defined by viral load ≥50 copies/mL measured at two consecutive visits, at least two weeks apart; • Change of ARV therapy • Death • Lost to follow up Unconfirmed viral load ≥50 copies/mL in the Week 24 window had another measurement two weeks later to confirm whether a virologic failure had occurred. The primary endpoint was reported in the 24 week report (U10-3028-01). Secondary efficacy endpoints included in this report are: • Proportion of virologic response (viral load <50 copies/mL) through EOT; • CD4+ cell counts and change from baseline through EOT.

Safety:	Safety endpoints included in this report are: • Adverse events (treatment related and unrelated); • Serious adverse events (including AIDS-defining events); • Occurrences of rashes and hepatic events; • Laboratory measurement abnormalities; • Change in laboratory test value between baseline and EOT; • Incidence of AIDS progression or death between baseline and EOT.
Statistical methods:	Descriptive statistics were provided for proportions of patients with virologic response and CD4+ cell counts at each visit time windows after Week 48. No hypothesis-based statistical testing was made among different treatment conditions.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	The proportions of major demographic subgroups were similar between the treatment groups. Overall, 85.7% of the patients were male with a mean age of 47.7 years; 91.6% were white; 7.2% were black. The primary endpoint was proportion of patients with sustained virologic response (viral load<50 copies/mL) through Week 24. For patients taking nevirapine XR, 93.6% had a sustained virologic response over 24 weeks versus 92.6% for patients taking nevirapine IR (95%CI = -4.3 to 6.2; > -12 = superior). Patients taking nevirapine IR had the option to change to nevirapine XR in the extension phase of the trial after Week 48, among which 93.1% observed viral loads < 50 copies/mL at their last available visits. For patients taking nevirapine XR who elected to participate in the extension phase, 94.6% of them observed viral loads < 50 copies/mL at their last available visits. The attrition rate for the study overall (378 out of total 443 patients had Week 144 viral loads reported) and for each of the treatment groups remained low through Week 144.

Safety results:	Over the 144 weeks of the trial the frequency of patients in each treatment group with various types of AEs was similar, with the nevirapine XR group tending to have slightly higher frequencies of AEs. This was especially true for patients who had investigator related AEs and AEs leading to discontinuation of study treatment. Post 48 week data showed that the frequency of various types of AEs was similar for nevirapine IR patients who switched to nevirapine XR after week 48 compared to patients who took nevirapine XR from the beginning of the study. Overall the most common AE in 1100.1526 was nasopharyngitis. Of the 18 AEs reported in >5% of patients over the 144 week duration of the trial, 8 of these AEs were indicative of infectious disease predominantly upper respiratory infection. In addition, 5 of these AEs were already associated with nevirapine. The most frequent AEs post week 48 were consistent with those reported over the 144 week duration of the trial. The majority of AEs were either mild or moderate in intensity. Grade 2, 3 or 4 ADRs were similar in frequency between treatment groups over the 144 weeks of the trial. The most common ADR was diarrhea. Less than 3% of patients discontinued treatment due to an AE over the 144 week duration of the trial. Four deaths occurred during 1100.1526. None of the deaths were related to nevirapine. Overall the frequency of SAEs was similar between treatment groups. The most common SAE was basal cell carcinoma seen in 7 (1.6%) patients. Overall patients who switched from nevirapine IR BID to nevirapine XR QD had a similar safety profile to those patients who remained on nevirapine IR during the trial. Post 48 weeks nevirapine IR patients who switched to nevirapine XR had similar frequencies of AEs to those patients dosed on nevirapine XR from the beginning of the trial.

Conclusions:	In conclusion a high response rate in regard to efficacy was maintained for patients who switched from a nevirapine IR based regimen to a nevirapine XR regimen after week 48. The patients who switched regimens at the start of the trial and also post week 48 continued on a new safe and well tolerated regimen. Safety findings reported here were similar to those observed after the last patient completed 48 weeks in the trial.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and results for primary and secondary endpoints of this open-label extension trial.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 3
Proportion of of patients with virologic response < 50 copies/mL after Week 48	Table 15.2.1:1
Proportion of of patients with virologic response < 400 copies/mL after Week 48	Table 15.2.1: 2
Change in VL from baseline at each visit	Table 15.2.1: 3
Change in CD4+ cell count from baseline at each visit;	Table 15.2.2: 1
AE summary (secondary safety endpoints) • Proportion of patients reporting AEs • Proportion of patients reporting SAEs • Proportion of patients reporting AEs by severity and action taken with regard to test drug • Discontinuations due to AEs	Table 15.3.2: 1

Table 15.1.1: 3 Disposition of patients through Week 48

	IR 200BID	XR 400QD	Total
Enrolled			499
Randomised	149	296	445
Treated [N (%)]	148 (100.0)	295 (100.0)	443 (100.0)
Completed Week 48 visit [N (%)]	142 (95.9)	281 (95.3)	423 (95.5)
Prematurely discontinued prior to Week 48 visit [N (%)]	6 (4.1)	14 (4.7)	20 (4.5)
Reasons for discontinuation [N (%)]			
Death or events leading to death	1 (0.7)	0 (0.0)	1 (0.2)
Adverse events			
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease/condition	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	5 (1.7)	5 (1.1)
Lost to follow-up	1 (0.7)	2 (0.7)	3 (0.7)
Consent withdrawn	1 (0.7)	2 (0.7)	3 (0.7)
Non compliance	1 (0.7)	2 (0.7)	3 (0.7)
Lack of efficacy*	1 (0.7)	1 (0.3)	2 (0.5)
Pregnancy*	1 (0.7)	2 (0.7)	3 (0.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)

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

Source data: Appendix 16.2, Listing 1.1 ctr\xtds.sas 21MAY2012

Table 15.2.1: 1 Proportion of virologic response using LLOQ=50 copies/mL after Week 48 by visit - full analysis set

	no. with response/total no.(%)			
Visit Week	IR/XR	IR	XR	Total
Week 48	125/130 (96.2)	11/ 12 (91.7)	268/276 (97.1)	404/418 (96.7)
Week 60	122/130 (93.8)	9/ 12 (75.0)	253/274 (92.3)	384/416 (92.3)
Week 72	124/130 (95.4)	9/ 9 (100.0)	265/271 (97.8)	398/410 (97.1)
Week 84	118/125 (94.4)	7/ 8 (87.5)	244/268 (91.0)	369/401 (92.0)
Week 96	117/124 (94.4)	9/ 9 (100.0)	242/263 (92.0)	368/396 (92.9)
Week 108	119/125 (95.2)	8/ 9 (88.9)	247/260 (95.0)	374/394 (94.9)
Week 120	112/121 (92.6)	7/ 8 (87.5)	235/258 (91.1)	354/387 (91.5)
Week 132	115/121 (95.0)	6/ 7 (85.7)	238/252 (94.4)	359/380 (94.5)
Week 144	115/121 (95.0)	7/ 7 (100.0)	238/250 (95.2)	360/378 (95.2)
Last available visit	121/130 (93.1)	11/ 13 (84.6)	261/276 (94.6)	393/419 (93.8)

Note: The 95% CI for IR/XR at Week 48 is (92.8, 99.5); for XR at Week 48 is (95.1, 99.1)
Note: The 95% CI for IR/XR at Week 144 is (91.2, 98.9); for XR at Week 144 is (92.6, 97.8)

Source data: Appendix 16.2, Listing 4.2 ctr\visitvlrsp.sas 03JUL2012

Table 15.2.1: 2 Proportion of virologic response using LLOQ=400 copies/mL after Week 48 by visit - full analysis set

	no. with response/total no.(%)			
Visit Week	IR/XR	IR	XR	Total
Week 48	128/130 (98.5)	11/ 12 (91.7)	276/276 (100.0)	415/418 (99.3)
Week 60	128/130 (98.5)	10/ 12 (83.3)	274/274 (100.0)	412/416 (99.0)
Week 72	129/130 (99.2)	9/ 9 (100.0)	271/271 (100.0)	409/410 (99.8)
Week 84	124/125 (99.2)	8/ 8 (100.0)	267/268 (99.6)	399/401 (99.5)
Week 96	124/124 (100.0)	9/ 9 (100.0)	262/263 (99.6)	395/396 (99.7)
Week 108	124/125 (99.2)	9/ 9 (100.0)	260/260 (100.0)	393/394 (99.7)
Week 120	121/121 (100.0)	8/ 8 (100.0)	258/258 (100.0)	387/387 (100.0)
Week 132	120/121 (99.2)	7/ 7 (100.0)	251/252 (99.6)	378/380 (99.5)
Week 144	121/121 (100.0)	7/ 7 (100.0)	250/250 (100.0)	378/378 (100.0)
Last available visit	127/130 (97.7)	11/ 13 (84.6)	274/276 (99.3)	412/419 (98.3)

Table 15.2.1: 3 Summary of HIV-1 viral load [copies/mL] and change from baseline by visit (TaqMan) - full analysis set

	IR/XR			IR		
Visit Week of OEP	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Week 48	130	97.8 (537.9)	47.0 (47.0, 47.0)	12	106.3 (205.5)	47.0 (47.0, 47.0)
Week 60	130	11052.2 (125415)	47.0 (47.0, 47.0)	12	142.0 (220.7)	47.0 (47.0, 49.5)
Week 72	130	1781.7 (19729)	47.0 (47.0, 47.0)	9	47.0 (0.0)	47.0 (47.0, 47.0)
Week 84	125	2848.3 (31301)	47.0 (47.0, 47.0)	8	51.1 (11.7)	47.0 (47.0, 47.0)
Week 96	124	49.2 (11.0)	47.0 (47.0, 47.0)	9	47.0 (0.0)	47.0 (47.0, 47.0)
Week 108	125	100.1 (573.6)	47.0 (47.0, 47.0)	9	55.9 (26.7)	47.0 (47.0, 47.0)
Week 120	121	49.7 (12.5)	47.0 (47.0, 47.0)	8	47.4 (1.1)	47.0 (47.0, 47.0)
Week 132	121	54.5 (62.8)	47.0 (47.0, 47.0)	7	51.0 (10.6)	47.0 (47.0, 47.0)
Week 144	121	50.6 (20.8)	47.0 (47.0, 47.0)	7	47.0 (0.0)	47.0 (47.0, 47.0)
Last available visit	130	4522.0 (36356)	47.0 (47.0, 47.0)	13	134.3 (213.1)	47.0 (47.0, 47.0)
Change from baseline						
Week 48	130	48.4 (536.9)	0.0 (0.0, 0.0)	12	58.4 (202.3)	0.0 (0.0, 0.0)
Week 60	130	11004.4 (125415)	0.0 (0.0, 0.0)	12	94.1 (218.5)	0.0 (0.0, 2.5)
Week 72	129	1747.0 (19806)	0.0 (0.0, 0.0)	9	0.0 (0.0)	0.0 (0.0, 0.0)
Week 84	125	2798.8 (31301)	0.0 (0.0, 0.0)	8	4.1 (11.7)	0.0 (0.0, 0.0)
Week 96	124	0.2 (17.7)	0.0 (0.0, 0.0)	9	0.0 (0.0)	0.0 (0.0, 0.0)
Week 108	125	53.1 (574.2)	0.0 (0.0, 0.0)	8	0.0 (0.0)	0.0 (0.0, 0.0)
Week 120	121	3.5 (42.7)	0.0 (0.0, 0.0)	8	0.4 (1.1)	0.0 (0.0, 0.0)
Week 132	121	10.2 (78.7)	0.0 (0.0, 0.0)	7	4.0 (10.6)	0.0 (0.0, 0.0)
Week 144	121	1.0 (24.5)	0.0 (0.0, 0.0)	7	0.0 (0.0)	0.0 (0.0, 0.0)
Last available visit	130	4472.6 (36357)	0.0 (0.0, 0.0)	13	86.4 (211.0)	0.0 (0.0, 0.0)

Table 15.2.1: 3 Summary of HIV-1 viral load [copies/mL] and change from baseline by visit (TaqMan) - full analysis set

XR	
N	Mean (SD)	Median (Q1, Q3)
276	49.3 (18.3)	47.0 (47.0, 47.0)
274	50.4 (15.4)	47.0 (47.0, 47.0)
271	48.4 (14.4)	47.0 (47.0, 47.0)
268	4191.9 (67801)	47.0 (47.0, 47.0)
263	139.4 (1458.4)	47.0 (47.0, 47.0)
260	49.0 (12.2)	47.0 (47.0, 47.0)
258	50.4 (14.9)	47.0 (47.0, 47.0)
252	51.4 (36.3)	47.0 (47.0, 47.0)
250	49.0 (12.2)	47.0 (47.0, 47.0)
276	4156.3 (66821)	47.0 (47.0, 47.0)
Change from baseline	
275	-4.3 (67.6)	0.0 (0.0, 0.0)
274	-1.8 (69.4)	0.0 (0.0, 0.0)
271	-4.9 (68.2)	0.0 (0.0, 0.0)
268	4140.1 (67801)	0.0 (0.0, 0.0)
263	168.4 (1974.7)	0.0 (0.0, 0.0)
260	-3.5 (70.6)	0.0 (0.0, 0.0)
257	-2.3 (71.0)	0.0 (0.0, 0.0)
252	-1.8 (79.0)	0.0 (0.0, 0.0)
250	-4.6 (70.9)	0.0 (0.0, 0.0)
276	4103.2 (66822)	0.0 (0.0, 0.0)

Table 15.2.2: 1 Summary of CD4+ count [cells/mm^3] and change from baseline by visit - full analysis set

	IR/XR			IR		
Visit Week of OEP	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Week 48	127	648.3 (233.8)	611.0 (482.0, 799.0)	11	686.7 (405.6)	607.0 (459.0, 716.0)
Week 60	128	620.6 (226.8)	594.5 (451.0, 762.5)	12	621.8 (416.2)	550.0 (346.5, 673.0)
Week 72	127	633.9 (227.9)	588.0 (477.0, 748.0)	9	731.7 (477.6)	599.0 (411.0, 666.0)
Week 84	125	650.5 (240.2)	612.0 (497.0, 778.0)	8	830.5 (553.9)	696.5 (453.5, 968.0)
Week 96	121	625.2 (233.0)	599.0 (476.0, 758.0)	8	733.1 (388.1)	656.5 (462.5, 959.5)
Week 108	125	645.9 (231.7)	613.0 (497.0, 775.0)	9	767.1 (458.6)	727.0 (452.0, 772.0)
Week 120	121	658.8 (233.1)	647.0 (487.0, 777.0)	8	759.5 (469.7)	679.0 (379.0, 957.0)
Week 132	120	636.5 (210.5)	630.5 (456.0, 779.0)	7	808.4 (518.6)	739.0 (343.0, 1054)
Week 144	120	660.3 (239.8)	625.5 (494.5, 803.0)	7	895.6 (753.0)	735.0 (293.0, 999.0)
Last available visit	130	642.0 (244.5)	607.5 (484.0, 799.0)	13	760.9 (566.9)	664.0 (464.0, 831.0)
Change from baseline						
Week 48	126	77.8 (142.8)	75.3 (-18.5, 158.5)	11	139.8 (126.9)	145.5 (40.0, 253.5)
Week 60	126	51.1 (138.1)	53.5 (-23.0, 118.5)	12	11.5 (138.4)	27.8 (-110.0, 114.0)
Week 72	126	61.3 (128.6)	69.3 (-7.0, 117.0)	9	77.9 (109.5)	62.5 (4.0, 135.0)
Week 84	123	80.3 (156.5)	71.5 (-14.0, 175.5)	8	134.6 (214.2)	88.8 (-15.8, 197.8)
Week 96	120	55.1 (156.7)	50.5 (-30.0, 144.0)	8	55.4 (80.7)	44.3 (-5.3, 111.5)
Week 108	124	72.4 (160.4)	66.3 (-16.5, 143.0)	8	117.4 (151.3)	145.8 (-7.0, 236.8)
Week 120	119	79.5 (168.4)	68.0 (10.0, 143.0)	8	90.0 (151.0)	69.0 (-28.3, 187.3)
Week 132	120	58.8 (153.6)	39.5 (-23.0, 153.0)	7	124.8 (158.7)	71.0 (23.5, 305.0)
Week 144	120	85.3 (151.6)	72.5 (-6.3, 179.3)	7	205.6 (388.6)	146.0 (-23.0, 264.0)
Last available visit	129	71.9 (157.1)	63.5 (-20.0, 164.0)	13	165.9 (302.5)	146.0 (-23.0, 253.5)

Table 15.2.2: 1 Summary of CD4+ count [cells/mm^3] and change from baseline by visit - full analysis set

XR	
N	Mean (SD) Median (Q1, Q3)
267	610.6 (255.3) 571.0 (443.0, 726.0)
273	613.3 (247.3) 585.0 (439.0, 725.0)
266	626.3 (247.9) 599.5 (462.0, 740.0)
267	612.8 (242.9) 593.0 (438.0, 754.0)
239	620.0 (234.5) 601.0 (470.0, 744.0)
256	627.8 (250.6) 599.0 (444.5, 777.0)
258	622.5 (278.6) 592.5 (439.0, 766.0)
252	627.2 (261.4) 604.0 (442.0, 758.0)
250	639.1 (250.1) 618.0 (464.0, 778.0)
276	641.6 (257.4) 612.0 (463.0, 782.5)
Change from baseline	
267	52.7 (143.5) 44.5 (-33.0, 127.5)
273	55.1 (136.5) 43.0 (-29.0, 124.0)
265	67.4 (141.5) 69.0 (-15.5, 139.0)
265	55.0 (130.9) 47.5 (-35.0, 142.5)
239	60.2 (130.3) 61.0 (-17.0, 146.5)
256	73.5 (151.0) 60.8 (-20.3, 154.8)
258	66.6 (182.3) 46.0 (-31.5, 139.5)
252	70.8 (146.7) 61.5 (-12.8, 154.3)
250	82.7 (157.4) 74.5 (-7.0, 159.5)
276	80.9 (163.5) 69.8 (-11.0, 161.5)

Table 15.3.2.1: 1 Adverse event overall summary - full analysis set

	IR 200BID N (%)	XR 400QD N (%)	All NVP N (%)
Number of patients	148 (100.0)	295 (100.0)	443 (100.0)
Patients with any AE	136 (91.9)	287 (97.3)	423 (95.5)
Patients with investigator defined drug-related AEs	10 (6.8)	48 (16.3)	58 (13.1)
Patients with AEs leading to discontinuation of trial drug	1 (0.7)	10 (3.4)	11 (2.5)
Patients with serious AEs	33 (22.3)	73 (24.7)	106 (23.9)
Fatal	2 (1.4)	2 (0.7)	4 (0.9)
Imm life-threatening	2 (1.4)	2 (0.7)	4 (0.9)
Disability/incap.	0 (0.0)	3 (1.0)	3 (0.7)
Req.hospitalisation	30 (20.3)	65 (22.0)	95 (21.4)
Prol.hospitalisation	0 (0.0)	2 (0.7)	2 (0.5)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (2.7)	9 (3.1)	13 (2.9)
Patients with DAIDS Grade 3 or 4 AEs	23 (15.5)	44 (14.9)	67 (15.1)
Patients with DAIDS Grade 4 AEs	3 (2.0)	12 (4.1)	15 (3.4)
Patients with any study drug-related DAIDS Grade 3 or 4 AEs	2 (1.4)	3 (1.0)	5 (1.1)
Patients with any study drug-related DAIDS Grade 4 AEs	0 (0.0)	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.1