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.

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: Viramune® (nevirapine)		**EudraCT No.:** 2005-004321-26	
Name of active ingredient: Nevirapine		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 DEC 2010	**Trial No. / U No.:** 1100.1452/ U10-3737-01	**Date of trial:** 20 Feb 2006 – 01 Sep 2008	**Date of revision:** Not applicable

Title of trial:	A Case-Control Toxicogenomics Study to identify Unique Genetic Polymorphisms in Patients who have experienced Symptomatic Hepatotoxicity or Severe Cutaneous Toxicity within the First 8 weeks of Nevirapine Therapy
Coordinating Investigator:	[redacted].
Trial sites:	Multicentre Study, cf. Appendix 16.1.4
Publication (reference):	Data from this study have not been published
Clinical phase:	IV
Objectives:	Identify the unique genetic polymorphisms that may identify patients at risk for developing symptomatic hepatotoxicity or severe cutaneous toxicity observed during the first 8 weeks of nevirapine therapy through analysis of peripheral blood mononuclear cell DNA samples from "cases" and "controls".
Methodology:	A non-interventional, retrospective, case-controlled (1:2) study with blood sample collection for genotyping.
No. of subjects:	300 Cases: 100 White, 100 Black, 100 Asian: (50 symptomatic hepatotoxicity cases and 50 severe cutaneous toxicity cases per race)
	600 Controls (matched)
planned:	entered: 900
actual:	enrolled: 1536
	entered: 889

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Diagnosis and main criteria for inclusion:	Male or female patients ≥18 years of age with HIV-1 infection who had received or were presently receiving nevirapine, and who met the definition of Case or Control **Case Patients**: Male or female patients ≥18 years of age with HIV-1 infection who experienced **one or more** of the following adverse reactions within the first 8 weeks of starting nevirapine therapy: • Grade 3 or 4 LFT elevation (ALT or AST > 5x ULN) with any symptom consistent with clinical hepatitis • Acute liver failure secondary to nevirapine therapy* • Functional group III or IV nevirapine related cutaneous toxicity *Acute liver failure is defined as serious liver injury usually requiring hospitalization that may lead to death or liver transplantation. **Control Patients:** Male or female patients ≥18 years of age with HIV-1 infection who had been exposed to nevirapine therapy for at least 18 weeks and who did **not** meet the case definition. Control patients were matched to case patients **by the sponsor** on: • Gender • Race • Baseline CD4 cell count ± 50 cells/mm^3 (prior to initiation of nevirapine therapy)
Test product: **dose:** **mode of admin.:** **batch no.:**	No test product used in this study
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	No reference therapy was used in this study

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Duration of treatment:	No drug treatment was given in this study
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy was not evaluated in this study
Safety:	Retrospective Serious Adverse Events and Adverse Events were collected. Prospective Serious Adverse Events were also collected.
Statistical methods:	Analyses explored associations between genotypes in candidate genes of pathways associated with drug metabolism, drug transporters, immune response, and nevirapine-associated hepatic and dermatologic adverse reactions. Cases and controls were compared using chi-squared tests. Logistic regression was used to explore multiple factors and their interactions. Additional exploratory methods were used as a means of identifying epistatic relationships between multiple loci.

SUMMARY – CONCLUSIONS:

Genomic Results:

HLA-B*35 is observed in 19.7% of Asian cutaneous cases and 6.5% of Asian controls. The association is strongest in the Thai subgroup, with odds ratio of 5.75.

HLA-Cw*15 is observed in 13.0% of White cutaneous cases and 3.3% of White controls, with odds ratio of 4.41.

HLA-Cw*04 is observed in excess in cutaneous cases for all races. The overall odds ratio is 2.48, with no significant heterogeneity among races (Breslow-Day p=0.228).

HLA-DRB1*01 is observed in 43.9% of White hepatic cases and 20.6% of White controls, with odds ratio of 3.02.

HLA-DQB*05 is observed in 52.6% of White hepatic cases and 32.4% of White controls, with odds ratio of 2.32.

Three SNPs out of the total of 2744 that were evaluable were associated with case control classification. All three are associated with CYP 2B6 and are also associated with cutaneous cases.

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For the B35+ Asian patients the Cw*04 status is associated with rash, with 82% (14/17) of Cw*04+ patients from the rash group and 0% (0/12) of Cw*04- patients from the control group. For the B35- Asian patients the Cw*04 status is not associated with rash, but the CYP 2B6 status is. The probability that a patient is from the rash group declines from 36% (10/28) with CYP 2B6++ to 23% (22/94) with +- to 17% (25/147) with --, Cochran-Armitage test p=0.024.

Safety results:

A total of 31 patients reported one or more serious adverse events (SAEs) during this trial. Seventeen of the 31 patients were cutaneous case or control patients who were entered into the trial. There were no SAEs reported for entered hepatic case patients. Fourteen of the 31 patients had signed patient informed consent but were not entered into the study as they did not proceed to visit 2 and were considered "screen failures." Appendix 16.2.7, Listing 7.2.1 details case, control and not entered patients. The patients listed below reported one or more SAEs and one patient [redacted] died.

Twenty nine patients of the 31 patients had SAEs that were unrelated to NVP use. Two patients reported SAEs that occurred while taking NVP. NVP was discontinued in both patients. The events deemed to be related to NVP use were drug eruption [redacted] and hepatitis [redacted]. Both patients recovered from their events.

Twenty of the 31 patients recovered from **all** of their events. Six patients [redacted] (basal cell carcinoma), [redacted] (Pneumothorax) [redacted] (atrial fibrillation), [redacted] (idiopathic thrombocytopenia purpura) [redacted] (weight decrease, affective disorder and sleep disorder) and [redacted] (B-cell lymphoma) did not recover from these events. One patient [redacted] had an outcome of sequelae for cerebral toxoplasmosis. One patient [redacted] died from their events (see Section 12.3.2). One patient had an outcome of unknown for an ovarian cyst [redacted] One patient [redacted] recovered from some of their events but had outcomes of sequelae for lipohypertrophy. One patient [redacted] did not recover from the events of idiopathic thyrombocytopenic purpura, lymphadenopathy, pyrexia, heptatosplenomegaly and had outcomes of sequelae for fatigue and anorexia.

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Conclusions:

Most previously reported relationships between HLA alleles and adverse reactions to nevirapine were replicated. Relationships between markers of slow clearance by the CYP 2B6 pathway and risk of cutaneous events were observed. Most relationships were found to be limited to one race and one of the adverse reactions that was investigated. These factors were only present for a relatively small fraction of the cases in this study, leading to the conclusion that they would not be practical screens for patients considering the use of nevirapine to treat HIV-1 infection.

In summary, most of the SAE's reported were moderate to severe in intensity, with the majority of SAEs (29) unrelated to NVP use. Most of the patients recovered from either all or some of their events with only a few patients not recovering from any of their events. One patient died from their events which were deemed to be unrelated to NVP use.