Clinical Study Synopsis for Public Disclosure

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<table>
<thead>
<tr>
<th>Name of company:</th>
<th>Boehringer Ingelheim</th>
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</thead>
<tbody>
<tr>
<td>Name of finished product:</td>
<td>Viramune XR tablets</td>
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<tr>
<td>Name of active ingredient:</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Module:</td>
<td></td>
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<td>Report date:</td>
<td>16 JAN 2013</td>
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<tr>
<td>Trial No. / U No.:</td>
<td>1100.1518 / U12-3932-01</td>
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<tr>
<td>Dates of trial:</td>
<td>04 JUN 2009 – 22 OCT 2012</td>
</tr>
<tr>
<td>Date of revision:</td>
<td>Not applicable</td>
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<tr>
<td>EudraCT No.:</td>
<td>2008-005855-61</td>
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</table>

Title of trial: An open-label, multiple dose, 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

Coordinating Investigator: M.D.

Trial sites: Multicentre Study, cf. Appendix 16.1.4

Publication (reference): Data from this study have not been published.

Clinical phase: I/Ia

Objectives: 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)

Methodology: PK phase was open-label, multiple dose, non-randomized, cross-over design; OEP was open-label, multiple dose, non-randomized

No. of subjects:

<table>
<thead>
<tr>
<th>planned:</th>
<th>enrolled: 100 (PK)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>entered: 75 (PK)</td>
</tr>
<tr>
<td>actual:</td>
<td>enrolled: 90 (PK)</td>
</tr>
<tr>
<td></td>
<td>entered: 85 (PK) and analysed for primary endpoint</td>
</tr>
<tr>
<td></td>
<td>3-&lt;6 yrs: 29</td>
</tr>
<tr>
<td></td>
<td>6-&lt;12 yrs: 28</td>
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<tr>
<td></td>
<td>12-&lt;18 yrs: 12</td>
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</table>
### Diagnosis and main criteria for inclusion:
HIV-1 infected children and adolescents 3-<18 years of age treated for at least 18 weeks with a Viramune (immediate release) IR based regimen and an undetectable viral load (VL <50 copies/mL) prior to enrollment. Patients were stratified into three groups according to age (3-<6 years, 6-<12 years, and 12-<18 years) and remained within that stratification throughout the trial.

### Test product:
Viramune XR tablets

dose: 200 mg, 300 mg or 400 mg QD
mode of admin.: Oral
batch no.: B083001027 (100 mg tablets), B083000135 (400 mg tablets)

### Reference therapy:
None

### Duration of treatment:
Patients received Viramune IR for at least 10 days (run-in) prior to the PK analysis. On Day 12, Viramune IR was switched to Viramune XR. All patients received Viramune XR for nine days prior to the collection of a nevirapine (NVP) concentration time profile for PK analysis. Every patient who completed the PK phase had the option to continue Viramune XR in the OEP if, in the Investigator’s opinion, the patient benefitted from the treatment. Treatment continued until the IND was withdrawn, Viramune XR was approved and available by prescription in a given country or the patient was enrolled in a compassionate use program.

### Criteria for evaluation:

#### Efficacy / clinical pharmacology:
Primary PK endpoints for the trial were previously reported (U10-3350). Secondary efficacy endpoints for at least 24 weeks of OEP treatment were previously reported (U11-3309). This final report includes cumulative efficacy and safety data from the start of the PK phase through the end of the OEP for:
- proportion of patients maintaining a VL <50 copies/mL
- change from baseline in mean CD4+ cell counts
and trough PK NVP concentration data from the end of the 24 week report through the end of the OEP.

#### Safety:
Adverse events (AEs), serious adverse events (SAEs), and laboratory measurements.
Statistical methods: Safety, efficacy and trough PK concentrations were analyzed descriptively. The following descriptive statistics were calculated for NVP trough concentrations: $C_{\text{pre,ss,N}}$: arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean and geometric coefficient of variation.

Efficacy and safety analyses were performed on 2 analysis sets: 1) treated set (TS), patients who took at least one dose of trial medication, including Viramune IR, and 2) full analysis set (FAS), patients who participated in the OEP. The unplanned treatment delay between the PK phase and OEP for some patients was taken into consideration for the analyses. Some patients were removed from the trial due to improper OEP informed consent. Once the informed consent language was approved by regulatory authorities, patients were allowed to re-enter the study. Patients who discontinued before approval of the OEP informed consent were not rescreened. In the TS analysis set, data obtained from the unplanned treatment delay were included. In the FAS, data obtained during the unplanned delay were excluded.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: There were 85 children (47 female and 38 male) 3–<18 years of age who took at least one dose of trial medication, including Viramune IR (TS); there were 40 children (22 female and 18 male) in the OEP (FAS): 28 from Botswana, 12 from Germany/US. 87.5% were Black. Key baseline characteristics related to HIV-1 disease were similar across the three age groups for both the TS and FAS.

No confirmed virologic failure was observed during the entire OEP.

Steady-state geometric mean trough plasma NVP concentrations were relatively stable over the weeks of study. Variability was considered acceptable for PK samples collected within a time window of 19 to 29 hours after the most recent intake of QD Viramune XR.
Safety results:
The overall mean duration of exposure to Viramune (included Viramune IR during the run-in phase and delay in the OEP, and Viramune XR during the PK phase and OEP) was 55.3 weeks (range: 0.1-155.4 weeks); median duration of exposure to Viramune XR QD during the OEP was 64.3 weeks (range: 9.7-152.4 weeks) and was similar in all three age groups. All 12 (100.0%) patients from Germany and the US continued directly into the OEP; median duration of exposure for US and German patients was 115.4 weeks (range: 96.7-152.4 weeks). The median duration of exposure was 64.1 weeks in the 28 Botswana patients (64.1 weeks in all 3 age groups) and reflects the treatment delay.

Overall, 69 (81.2%) patients reported at least 1 AE. AEs were DAIDS Grade 1 in 66 (77.6%), Grade 2 in 26 (30.6%), and Grade 3 in 4 (4.7%) patients. There were no Grade 4 events or Grade 3 or 4 events defined as study-drug related. There were no deaths.

Overall, the most frequently reported AEs (by system organ class) were infections and infestations in 54 (63.5%) patients, respiratory, thoracic and mediastinal disorders in 34 (40.0%) patients, and skin and subcutaneous tissue disorders in 30 (35.3%) patients. The most frequently reported AEs (by preferred term) were upper respiratory tract infections and cough.

Seven (8.24%) patients (2 in the 3-<6 year group, 5 in the 12-<18 year group) reported drug-related rashes during treatment with Viramune XR; all were Grade 1 or 2 and none limited treatment.

Five patients had trough NVP concentrations >12,000 ng/mL; there were no safety concerns in these patients (all AEs in those patients were consistent with the Viramune XR AE profile).

No patients experienced hepatitis symptoms, symptoms associated with hepatic events or hypersensitivity reaction.

No clinically relevant changes were observed in blood pressure or pulse rate during treatment. There were no Grade 3 or 4 laboratory abnormalities in hematology parameters, total bilirubin, transaminases, creatinine, sodium, lipids, or lipase levels. Abnormal electrolyte values (Grade 3 or 4) were rarely observed and were not clinically relevant.
### Synopsis

- **Name of company:** Boehringer Ingelheim
- **Tabulated Trial Report**
- **Name of finished product:** Viramune XR tablets
  - **EudraCT No.:** 2008-005855-61
- **Name of active ingredient:** Nevirapine
- **Module:**
- **Report date:** 16 JAN 2013
- **Trial No. / U No.:** 1100.1518 / U12-3932-01
- **Dates of trial:** 04 JUN 2009 – 22 OCT 2012
- **Date of revision:** Not applicable

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### Conclusions:

The efficacy, PK and safety profile of Viramune XR tablets administered QD in doses of 200, 300 or 400 mg in HIV-1 infected children three to <18 years of age is consistent across age groups and consistent with the profile in HIV-1 infected adults. The Viramune XR tablet formulation was effective in maintaining viral suppression and was well tolerated in all pediatric age groups. The results of this study indicate no safety concerns for the daily administration of Viramune XR tablets for up to 152 weeks in children as young as three years of age.