Steady State Evaluation of Two Extended Release (XR) Nevirapine (NVP) Tablets 400 mg QD Compared with Immediate Release (IR) NVP Tablets 200 mg BID in HIV-1 Infected Patients


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Pharmacokinetics
The relative bioavailability compared with NVP IR (based on gMean ratios of AUC0-24) was 89% (90% CI 75.3 - 98.7) for NVP XR 25% and 71% (90% CI 63.3 - 84.7) for NVP XR 20%. Group B (XR 20%) showed greater inter-individual variability in plasma concentrations of NVP XR Group A (XR 25%).

Compared with NVP IR (Table 2), both NVP XR formulations resulted in: longer tmax, lower Cmin and similar Cmax (90%CI 91.8 – 108.6%) for NVP XR 25%, but lower Cmax (78.9% [90%CI 67.2 – 93.5%] for NVP XR 20%

NVP concentration-time profiles of both XR formulations exhibited less fluctuation than for NVP IR (Figures 1 and 2).

Results
Demographics
Demographic characteristics were similar in treatment groups. Table 1. Demographic characteristics of study subjects

Table 1. Demographic characteristics of study subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (XR 25%)</th>
<th>Group B (XR 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)*</td>
<td>45.2 (7.9)</td>
<td>44.0 (8.4)</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>173.7 (7.9)</td>
<td>176.0 (7.5)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>74.0 (11.8)</td>
<td>71.8 (10.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>23.5 (2.5)</td>
<td>23.2 (3.0)</td>
</tr>
</tbody>
</table>

*Mean (standard deviation)

Conclusions
Both NVP XR formulations were safe and well tolerated. Administration of NVP XR 400 mg QD resulted in extended absorption and reductions in peak levels at steady state while attaining similar troughs. The XR 25% formulation exhibited better bioavailability and variability than the XR 20% and was selected for further development.

References
1. Flaharty KK, Hall D, Scherer J, MacGregor T, Jelaska A, Robinson P. Nevirapine and efavirenz plasma conc. [ng/mL] and correlation with viral load and virologic resistance in subjects from the 2NN study. 110001 - 110001; 110001 - 110001.

Figure 1: Plasma concentration of NVP in group A after NVP XR 400 mg QD compared with NVP IR 200 mg BID

Figure 2: Plasma concentration of NVP in group B after NVP XR 400 mg QD compared with NVP IR 200 mg BID

Table 2. Pharmacokinetic parameters of NVP XR compared with NVP IR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (N=24)</th>
<th>Group B (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24 [ng·h/mL]*</td>
<td>22500 (210)</td>
<td>13000 (205)</td>
</tr>
<tr>
<td>Cmax [ng/mL]*</td>
<td>6100 (22)</td>
<td>5650 (15)</td>
</tr>
<tr>
<td>Cmin [ng/mL]*</td>
<td>2150 (15)</td>
<td>2450 (7)</td>
</tr>
</tbody>
</table>

*Mean (coefficient of variation)

Safety
Adverse events (AEs), clinical laboratory, viral load at each visit (every 3 days).

• Administration of NVP XR 400 mg QD resulted in extended absorption and reductions in peak levels at steady state while attaining similar troughs as NVP IR.

• Adverse events were usually mild (42%) and uncommon (5%). Subjects in each group had an AE which was considered drug-related: diarrhea with XR 25% and increased Hb/Hct (0.5%) with XR 20%

• No clinically relevant changes in laboratory values (including transaminase elevations) were observed.

• No virologic failures were observed.

• Based on these findings, NVP XR 25% was selected for further development.

Methods
This clinical trial was an international, open-label, multi-center, parallel group, crossover study. Eligible subjects were males and females infected with HIV-1, fully suppressed to <50 c/mL at screening who had been treated for >12 weeks with a stable regimen containing NVP 200 mg BID without protease inhibitors.

After entering the study, subjects continued treatment with NVP IR 200 mg BID for an additional 3 days (inference treatment). Then subjects were switched to one of the two NVP XR 400 mg QD formulations (25% or 20%) for 19 days (test treatment). Plasma samples were taken for 26 h following the last dose of each treatment.

Trial Endpoints:
- AUC0-24 --- to define relative bioavailability
- Cmax/Cmin ratio --- as other pharmacokinetic parameters

- Adverse events (AEs), clinical laboratory, viral load at each visit (every 3 days)

Conclusion
Adherence is important in preventing treatment failure and drug resistance in HIV therapy (1-2). Once daily (QD) dosing is preferred to improve compliance. Vitamains (NVP IR) 200 mg tablets are given daily (IR) as part of combination therapy for HIV-1 infection. Boehringer Ingelheim developed two extended release formulations of NVP (identified as XR 25% and XR 20%) to allow QD dosing as a means of improving therapy with Viramune.

This study compared the relative bioavailability at steady state of each NVP XR formulation with that of NVP IR in subjects infected with HIV-1.