Bioavailability of Extended-Release Nevirapine 400 and 300 mg in HIV-1: A Multicenter, Open-Label Study

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ABSTRACT

Background: Nevirapine (NVP) is a widely used non-nucleoside reverse transcriptase inhibitor. A once-daily extended-release (XR) formulation would potentially increase adherence and thus efficacy.

Objective: The aim of this study was to investigate the steady-state bioavailability of 2 once-daily tablet formulations of NVP XR (containing 25% or 20% hypromellose; NVP XR25 and NVP XR20, respectively) in 400- or 300-mg tablets compared with twice-daily immediate-release (IR) NVP 200-mg tablets.

Methods: This Phase Ib multinational, multicenter, open-label trial was conducted in patients aged 18 to 60 years, infected with HIV-1 (viral load, ≤50 copies/mL), and treated for ≥12 weeks with twice-daily NVP IR 200 mg. Patients were switched to NVP XR25 400 or 300 mg or NVP XR20 400 or 300 mg for 19 days. Plasma samples were collected over 24-hour periods at steady state. Primary end points were $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{min,ss}$, analyzed using an ANOVA statistical model on the logarithmic scale and 2-sided 90% CI. Sample size was determined assuming an intrasubject %CV of 20% for C_{max}. Adverse events (AEs) and viral loads were monitored.

Results: Ninety-two patients were enrolled (NVP XR25 400 mg, 24 patients; NVP XR20 400 mg, 24; NVP XR25 300 mg, 21; NVP XR20 300 mg, 23). Compared with NVP IR, the $AUC_{0-24,ss}$ values of the NVP XR formulations were lower (test/reference ratios: 79.5% [90% CI, 73.0–86.7; $P = 0.544$], 71.0% [90% CI, 63.3–79.7; $P = 0.956$], 90.3% [90% CI, 80.4–101.4; $P = 0.044$], and 83.7% [90% CI, 77.9–89.9; $P = 0.148$] with NVP XR25 400 mg, NVP XR20 400 mg, NVP XR25 300 mg, and NVP XR20 300 mg, respectively). The relative bioavailability of NVP XR25 was greater compared with that of NVP XR20. $C_{max,ss}$ values were lower with all NVP XR formulations compared with NVP IR. For $C_{min,ss}$, NVP XR25 400 and 300 mg were not significantly different from NVP IR, with 90% CIs within the range of 80% to 125% ($P = 0.039$ and $P = 0.017$, respectively). All AEs were mild or moderate, with no significant differences between treatment groups. No virologic failures (viral load, >50 copies/mL over 2 consecutive readings) were observed.

Conclusions: Extent of bioavailability was lower and $t_{max,ss}$ was delayed with all NVP XR formulations compared with NVP IR. The bioavailability of the NVP XR25 formulations was greater than that of the NVP XR20 formulations. $C_{min,ss}$ with NVP XR25 was similar to that with NVP IR. All of the NVP XR formulations were well tolerated. The

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400-mg NVP XR25 formulation was selected for further development. (*Clin Ther.* 2011;33:1308–1320)

Key words: bioavailability, bioequivalence, clinical trial, delayed-action preparations, HIV-1, nevirapine, non-nucleoside reverse transcriptase inhibitors, pharmacokinetics.

INTRODUCTION

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been reported to be effective in the treatment of infection with HIV-1. Resistance to NNRTIs has been associated with poor adherence, which adversely affects the maintenance of viral suppression (defined as an HIV-1 viral load <50 copies/mL).[1]

NVP is available as an immediate-release (IR) tablet of 200 mg taken twice daily. The use of a once-daily extended-release (XR) formulation of NVP was approved on March 25, 2011, in the United States, and has been submitted for approval to the European Medicines Agency. Once-daily treatments have been reported to be more convenient and to improve adherence.[2] For these reasons, the steady-state pharmacokinetic properties of once-daily NVP IR were examined in a Phase I, randomized study in 20 patients.[3] That study reported that steady-state exposure to NVP ($AUC_{0-24,ss}$) was not significantly different between NVP IR 400 mg once daily and NVP IR 200 mg twice daily ($P = 0.60$); however, the peak and trough plasma NVP concentrations were significantly higher and lower, respectively, with once-daily administration compared with twice-daily administration ($C_{max,ss}$, 6.7 vs 5.4 μg/mL, respectively [$P = 0.03$]; $C_{min.ss}$, 2.9 vs 3.7 μg/mL [$P < 0.01$]).

These findings suggested that a once-daily XR formulation would be a useful therapeutic option. Such a formulation might improve treatment adherence and compliance and allow dosing symmetry with once-daily fixed-dose combinations of preferred nucleos(t)ides, such as tenofovir DF/emtricitabine. Consequently, 2 tablet formulations of NVP XR were developed at 300- and 400-mg doses. These XR formulations were developed using hypromellose 2208, a hydrophilic polymer, with the objective of providing extended, controlled release of NVP in the gastrointestinal tract. Depending on the relative ratio of hypromellose 2208 used in the production process, different NVP XR tablet formulations have been developed and evaluated in healthy volunteers.[4] An in vitro–in vivo correlation (IVIVC) for 3 tablet formulations of NVP XR with varying polymer contents was developed. This Level A IVIVC represents a point-to-point relationship between in vitro dissolution and the in vivo input rate for NVP XR formulations providing robust predictions of in vivo profiles based on in vitro dissolution profiles.[4]

The present study investigated the pharmacokinetic properties and tolerability profiles of 2 tablet formulations of NVP XR (containing 25% or 20% hypromellose; NVP XR25 and NVP XR20, respectively). These 2 formulations were selected based on IVIVC and steady-state modeling that suggested that they were likely to have the most suitable pharmacokinetic and tolerability profiles.[4] NVP XR20 and NVP XR25 were administered at doses of 300 and 400 mg.

PATIENTS AND METHODS

Study Design and End Points

This Phase Ib, open-label, nonrandomized-sequence, parallel-group trial was conducted from December 2006 to May 2007 at 17 sites (9 in Germany, 4 in France, 3 in the United States, and 1 in Switzerland). All of the sites were clinics that were qualified to perform Phase I studies.

The primary end points were the following pharmacokinetic parameters: $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{min,ss}$. Another primary objective was to assess the effects of food on the relative bioavailability of NVP XR.

The secondary end point was the tolerability of NVP (based on adverse events [AEs], clinical laboratory testing, vital sign measurements, 12-lead ECG, viral load, and assessment of tolerability by the investigator). Global tolerability, assessed by the investigator after specifically asking the patients to rate treatment tolerability, was classified as "good," "satisfactory," "not satisfactory," or "bad." The following NVP pharmacokinetic parameters were also secondary end points: $C_{max,ss}/C_{min,ss}$ ratio, percentage of peak–trough fluctuation of plasma NVP concentration over 1 dosing interval at steady state, t_{max} at steady state ($t_{max,ss}$), mean plasma NVP concentration at steady state (C_{avg}), and the apparent clearance of NVP in plasma at steady state.

The clinical trial protocol was reviewed and approved by local independent ethics committees. Written informed consent was obtained before screening and participation in the trial. The trial was conducted