Multiple-Dose Treatment with Rifabutin Reduces the Exposure of Doravirine

Introduction

- Doravirine (MK-1439) is a novel, potent, once-daily non-nucleoside reverse transcriptase inhibitor (NNRTI) in development for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral therapies.
- Doravirine is primarily metabolized by oxidation via cytochrome P450 3A4 (CYP3A4). Therefore, a potential exists for drug interactions mediated by CYP3A4 inhibitors and inducers.
- Rifabutin, a strong CYP3A4 inducer, may be prescribed for HIV patients co-infected with Mycobacterium tuberculosis (M. tuberculosis).
- A previous clinical trial demonstrated that co-administration of doravirine with multiple-dose rifampin resulted in decreased doravirine exposure.
- Results suggested that the two agents should not be co-administered, even with doravirine dose adjustment.
- Rifabutin is considered to be a more moderate inducer of CYP3A4 and may be a viable therapeutic alternative for patients with HIV under concomitant treatment for tuberculosis.
- This study evaluated the effect of rifabutin co-administration on the pharmacokinetics (PK) of doravirine.

Objectives

- This study was undertaken to evaluate the effect of multiple doses of rifabutin on single-dose doravirine PK parameter in healthy subjects (primary objective).
- The secondary objective of the study was evaluation of the safety and tolerability of doravirine and with and without rifabutin.

Methods

- This study was an open-label, 2-period, 2-treatment, fixed-sequence PK drug-drug interaction study in healthy male and female subjects 18-65 years of age (Protocol No. MK-1439-035).
- The trial was conducted in compliance with Institutional Review Board/Independent Ethics Committee and International Conference on Harmonization Good Clinical Practice Guidelines and all subjects provided informed consent.
- The study design is summarized in Figure 1.

Figure 1. Study design – protocol MK-1439-035

- Treatment cohort P1 received a single oral dose of doravirine 100 mg on Day 0, in Period 1 (P1), followed by a 7-day washout. Doravirine 300 mg was co-administered on Day 14 with rifabutin on Day 14.

PK assessments

- Plasma samples for doravirine concentration measurements were collected through 72 hours post-dose in P1 and P2.
- In each period, 12 samples were collected prior to doravirine dose (0 hour) and at 0.5, 1, 2, 4, 6, 12, 24, 36, 48, and 72 hours after rifabutin co-administration.
- PK parameters estimated for the primary objective included: peak plasma concentration (Cmax) within the concentration-time curve from time zero to infinity (AUCINF), and concentration at 24 hours post-dose (C24).
- Other PK parameters estimated included trough plasma concentration (C18), area under the concentration-time curve from time zero to 12 hours (AUC12), and apparent clearance during the terminal phase during the dosing period (CL/F).

Safety

- Safety was assessed through the following measures:
  - Adverse events (AEs)
  - Laboratory evaluations (hematology and chemistry)
  - Vital signs and ECGs

Statistical analyses

- Individual values for C18, AUC12, and C24 for doravirine were natural log-transformed and evaluated separately using a linear mixed-effects model with fixed-effects terms for treatment.
- A-priori 90% confidence interval (CI) for the true mean difference (rifabutin + doravirine – doravirine alone) for doravirine C18, AUC12, and C24 on the log scale was computed from the linear mixed-effects model.
- The clearance was represented by 90% CI for the true geometric mean ratios (rifabutin + doravirine/doravirine alone) for doravirine Cmax, AUC0–C24, AUC0–last, and CL/F.

Results

Subject disposition

- Eighteen healthy subjects (15 males) were enrolled and 12 completed the study – subject disposition is summarized in Table 1.
- Six subjects discontinued the study as follows:
  - Five in P1 prior to rifabutin administration due to fever with or without other flulike signs and symptoms.
  - One in P1 at the discretion of the principal investigator.

Table 1. Subject disposition


Plasma concentration-time profile of doravirine

- Doravirine plasma concentration (mean ± standard deviation [SD]) profiles are provided in Figure 2.

PK of doravirine

- Following co-administration with multiple-dose rifabutin, doravirine C24 and Cmax values were reduced by approximately 10% and 8%, respectively (Table 2).

Discussion

- The reduction in doravirine AUC is consistent with the inhibitory effect of rifabutin on CYP3A4.
- The inhibitory effect of rifabutin is also reflected in the increased CL/F of doravirine in the presence of rifabutin (1.22 L/h compared to 0.54 L/h when administered as monotherapy) – an expected and for a moderate inhibitor; this effect was not as large as that observed for rifampin.
- Consistent with increased CL/F, the C18, of doravirine was shortened from 15.7 hours to 5.4 hours after treatment with rifabutin.
- Following co-administration of doravirine and rifabutin, doravirine C24 exceeded the PK target (79 nM) based on efficacy against the wild-type virus in vitro (data in file).
- Furthermore, based on inter-subject variability in C24 values for the 25 mg dose in a Phase 2 study, efficacy based on viral load suppression at Week 24 was observed in subjects with trough levels as low as 107 nM.

Conclusions

- Administration of doravirine alone and after multiple doses of rifabutin was generally well tolerated.
- Multiple-dose rifabutin reduced doravirine AUC by 50% and C24 by 69% via CYP3A4 induction, as compared with doravirine alone. Doravirine C24 was similar when administered either alone or with multiple doses of rifabutin.
- The clinical implications of these effects need to be assessed within the broader context of doravirine PK, safety, and efficacy data.

Table 2. Doravirine plasma pharmacokinetics – summary statistics following administration of a single oral dose of doravirine 100 mg alone or after rifabutin 300 mg daily for 14 days to healthy male and female subjects

![Table 2](image_url)

References


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