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Effect of Ketoconazole on the Pharmacokinetics of Doravirine (MK-1439), a Novel Non-Nucleoside Reverse Transcriptase Inhibitor for the Treatment of HIV-1 Infection

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Introduction

- Doravirine (MK-1439) is a novel, well-tolerated, once-daily, non-nucleoside reverse transcriptase inhibitor in development for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral therapy (ART).
- Preclinically, doravirine is a potent inhibitor of HIV-1 wild-type virus and the K103N, Y181C, and K103N/Y181C mutant viruses.[1]
- In a 48-week study in combination with TRUVADA™ (emtricitabine/tenofovir), doravirine has been shown to be efficacious in treating ART-naïve HIV-1-infected patients over the investigated 25-200 mg dose range.[2]
- The anticipated clinical dose of doravirine is 100 mg administered once daily.
  - Doravirine is primarily metabolized by oxidation via CYP3A4, shows no inhibitory or inductive potential on CYP3A4-mediated metabolism *in vivo*, and is not an inducer or inhibitor of major CYP enzymes or transporters.[3] Doravirine was also shown to be a substrate, but not an inhibitor of, human P-glycoprotein (P-gp).[3]
- Modest increases in doravirine maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}), as well as significant elevations in plasma concentration at 24 hours (C_{24h}) and total area under the plasma concentration-time curve ($AUC_{0-\infty}$) and longer terminal half-life ($t_{½}$) were observed when doravirine was co-administered with ritonavir,[4] a clinical inhibitor and inducer of CYP3A4 and an inducer of glucuronidation.
- The antifungal ketoconazole is a potent inhibitor of CYP3A4 and the P-gp transporter[5] and was, therefore, used in this study to probe the interaction of doravirine with these pathways.

Objective

- To assess the effect of multiple doses of ketoconazole on the single-dose plasma pharmacokinetic (PK) profile of doravirine.

Methods

Study Design

- This was an open-label, 2-period, fixed-sequence study.
  - In Period 1, subjects received a single oral dose of 100 mg doravirine on Day 1. Following a washout of at least 7 days, subjects received oral doses of 400 mg ketoconazole once daily for 10 days (beginning Day 1 of Period 2), with co-administration of a single oral dose of 100 mg doravirine on Day 2 of Period 2.
- Blood samples for determination of doravirine concentrations were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 6, 12, 24, 30, 48, and 72 hours following the single dose of doravirine in Period 1, and at pre-dose and at 1, 1.5, 2, 3, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours following the single dose of doravirine in Period 2.
- Safety evaluations, including vital signs, electrocardiogram (ECG), laboratory assessments (hematology, biochemistry, and urinalysis) and adverse-event (AE) monitoring, were conducted throughout the study.

Study Population

- Healthy subjects, aged 19-50 years inclusive, were enrolled. Subjects using drugs or substances known to be significant inhibitors of CYP enzymes or significant inhibitors or substrates of P-gp were excluded from the study.

Statistical Analysis

- PK parameters ($AUC_{0-\infty}$, C_{max}, and C_{24h}) were natural-log–transformed prior to analysis and evaluated using a linear mixed-effects model with a fixed-effect term for treatment.
  - An unstructured covariance matrix allowed for unequal treatment variances and to model the correlation between the two treatment measurements within the same subject.
- The 90% confidence intervals (CIs) were generated for the geometric mean ratios (GMRs; doravirine + ketoconazole/doravirine alone) for the $AUC_{0-\infty}$, C_{24h}, and C_{max} of doravirine.

Results

Subject Disposition

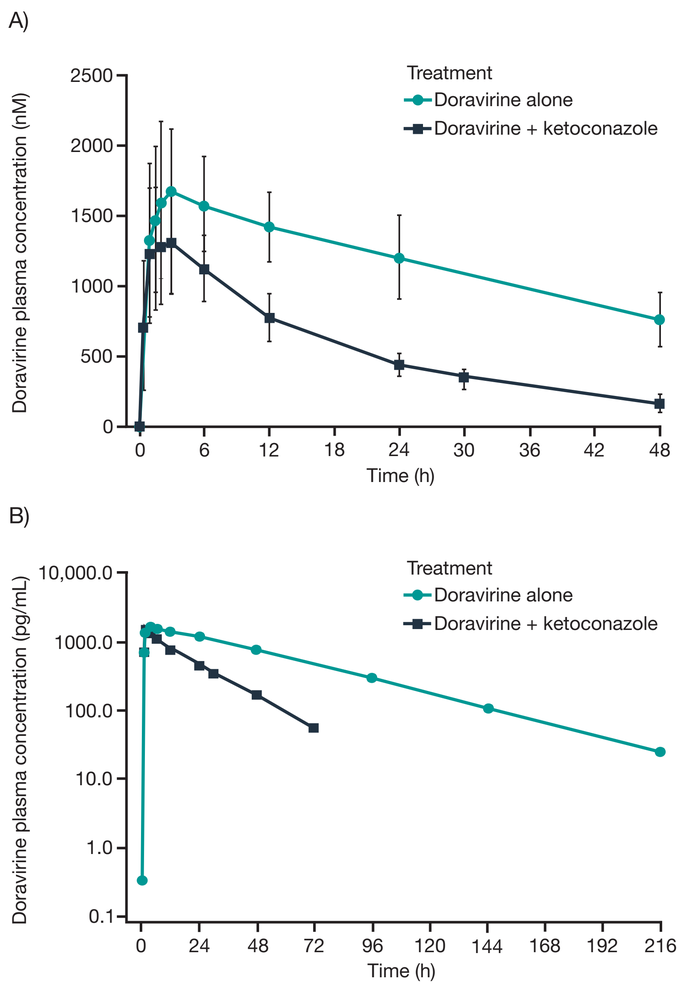
Table 1. Subject Disposition

	Overall N=10
Enrolled, N (%)	10 (100)
Male, n (age range, years)	8 (22–50)
Female, n (age range, years)	2 (48–49)
Completed, n (%)	10 (100)
Discontinued, n (%)	0

Plasma PK for Doravirine

- The mean C_{max} for doravirine (1402 nM) increased after co-administration with ketoconazole (to 1759 nM) (Figure 1 and Table 2).
- Doravirine $AUC_{0-\infty}$, C_{max}, and C_{24h} were increased by co-administration with ketoconazole (Table 2).

Figure 1. Arithmetic Mean Doravirine Plasma Concentration Profiles With and Without Co-administration with Ketoconazole: A) Linear Scale (±SD) and B) Semi-log Scale



SD, standard deviation.

Table 2. PK Parameters for Doravirine

PK parameter	Doravirine alone[a]			Doravirine + ketoconazole[b]			Doravirine + ketoconazole/ doravirine alone	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$[c] (μM•h)	10	29.88	(26.61, 33.56)	10	91.47	(76.36, 109.56)	3.06	(2.85, 3.29)
C_{max}[c] (nM)	10	1402.12	(1160.00, 1694.77)	10	1759.00	(1460.93, 2117.89)	1.25	(1.05, 1.49)
C_{24h}[c] (nM)	10	429.51	(382.57, 482.21)	10	1180.14	(991.41, 1404.80)	2.75	(2.54, 2.98)
T_{max}[d] (h)	10	2.00	(1.00, 6.00)	10	3.00	(1.00, 24.00)	–	–
Apparent terminal $t_{½}$[e] (h)	10	15.23	28.09	10	32.37	12.54	–	–

$AUC_{0-\infty}$,total area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{24h}, plasma concentration at 24 hours; GM, geometric least-squares mean; GMR, geometric least-squares mean ratio; LSM, least-squares mean; PK, pharmacokinetic; QD, once daily; T_{max}, time to reach maximum plasma concentration.
[a]Single oral dose of 100 mg doravirine (1 x 100 mg tablet) following an overnight fast.
[b]Multiple oral doses of 400 mg ketoconazole (2 x 200 mg tablets) QD for 10 consecutive days and a single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 2 following an overnight fast.
[c]Back-transformed LSM and CI from linear mixed-effects model performed on natural-log–transformed values.
[d]Median (min, max) reported for T_{max}.
[e]Geometric arithmetic mean and percent geometric coefficient of variation reported for apparent terminal $t_{½}$.

- In comparing a single dose of 100 mg doravirine co-administered with multiple doses of 400 mg ketoconazole versus a single dose of 100 mg doravirine alone, the GMRs for doravirine + ketoconazole/doravirine alone (90% CI) were 3.06 (2.85, 3.29) for $AUC_{0-\infty}$, 1.25 (1.05, 1.49) for C_{max}, and 2.75 (2.54, 2.98) for C_{24h} (Table 2).
- Geometric mean $t_{1/2}$ increased from 15.23 hours with doravirine alone to 32.37 hours in the presence of ketoconazole, consistent with a decrease in clearance due to inhibition of CYP3A4 metabolism (Table 2).

Safety

- No serious clinical or laboratory AEs were reported during the study.
  - Six subjects reported a total of 18 AEs, 13 of which were considered drug-related (6 related to doravirine only, 5 related to ketoconazole only, and 2 related to both doravirine and ketoconazole); all were judged by the investigator as mild in intensity and transient; none led to discontinuation.
  - All drug-related AEs occurred during Period 2. The drug-related AEs (occurrence, drug) were:
    - nausea (1, ketoconazole; 1, doravirine; 2, both)
    - headache (1, ketoconazole; 1, doravirine)
    - papular rash (2, doravirine)
    - insomnia (1, ketoconazole)
    - restlessness (1, ketoconazole)
    - rhinorrhea (1, ketoconazole)
    - papule (1, doravirine)
    - pruritus (1, doravirine).
  - No clinically significant changes were observed in laboratory values, vital signs, or ECG safety parameters.

Conclusions

- Doravirine single-dose plasma exposure was increased by co-administration with ketoconazole. Doravirine plasma $AUC_{0-\infty}$ and $t_{½}$ increased by approximately 3-fold and 2-fold, respectively, primarily by reducing the rate of CYP3A-mediated clearance.
  - The minimal increase in C_{max} suggests that P-gp inhibition does not impact the absorption of doravirine.
- The increase in doravirine exposure observed in this study is similar to the effect of ritonavir on doravirine,[2] suggesting that a significant proportion of doravirine metabolism in humans proceeds through CYP3A4.
  - Alignment of doravirine plasma PK changes with those observed upon co-administration of doravirine with ritonavir suggests that pathways other than CYP3A4 metabolism are not a clinically significant route of doravirine elimination in humans.
- Single oral doses of doravirine were generally well tolerated when administered alone or in combination with multiple oral doses of ketoconazole in the healthy subjects.
- These changes in doravirine exposure are likely not clinically meaningful based on available safety data to date and the lack of an exposure-response relationship for efficacy or safety up to a dose of 200 mg in a Phase 2 study.[3]
- These findings do not warrant restrictions on the use of potent CYP3A inhibitors in Phase 3 trials of doravirine.

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