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Multiple-Dose Treatment with Rifabutin Reduces the Exposure of Doravirine

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Introduction

- Doravirine (MK-1439) is a novel, potent, once-daily non-nucleoside reverse transcriptase inhibitor[1,2] 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)[3]; therefore, a potential exists for drug interactions mediated by CYP3A4 inhibitors and inducers
- Rifampin, a strong CYP3A4 inducer[4], may be prescribed to HIV patients co-infected with *Mycobacterium tuberculosis*[5]
  - A previous clinical trial demonstrated that co-administration of doravirine with multiple-dose rifampin resulted in decreased doravirine exposure[2]
  - 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[6]
- This study evaluated the effect of rifabutin co-administration on the pharmacokinetics (PK) of doravirine

Objectives

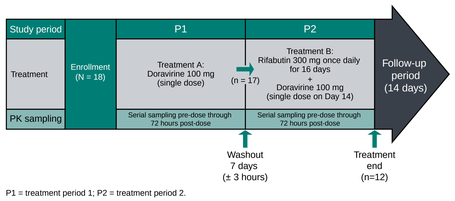
- This study was undertaken to evaluate the effect of multiple doses of rifabutin on single-dose doravirine PK parameters in healthy subjects (primary objective)
  - The secondary objective of the study was evaluation of the safety and tolerability of doravirine with and without rifabutin

Methods

Study design

- This 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



P1 = treatment period 1; P2 = treatment period 2.

Subjects

- Enrolled subjects were healthy based upon medical history, physical examination (including vital signs), a 12-lead electrocardiogram (ECG), and clinical laboratory tests performed at screening

Treatments

- In Period 1 (P1), a single dose of doravirine 100 mg was administered on Day 1; in Period 2 (P2), following a 7-day washout, rifabutin 300 mg was administered once daily for 16 days – doravirine 100 mg was co-administered 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, 3, 4, 6, 12, 24, 36, 48, and 72 hours after doravirine administration
- PK parameters estimated for the primary objective included: peak plasma concentration (C_{max}), area under the concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), and concentration at 24 hours post-dose (C_{24})
  - Other PK parameters estimated included time to peak plasma concentration (T_{max}), AUC from time 0 to time of last quantifiable sample (AUC_{0-last}), apparent terminal half-life ($t_{½}$), apparent clearance (CL/F), and apparent volume of distribution during the terminal phase after dosing (V_d/F)

Safety

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

Statistical analyses

- Individual values for C_{max}, $AUC_{0-\infty}$, and C_{24} for doravirine were natural log-transformed and evaluated separately using a linear mixed-effects model with fixed-effects term for treatment
- A 2-sided 90% confidence interval (CI) for the true mean difference (rifabutin + doravirine – doravirine alone) for doravirine C_{max}, $AUC_{0-\infty}$, and C_{24} on the log scale was computed from the linear mixed-effects model
- 90% CIs were exponentiated to obtain 90% CIs for the true geometric mean ratios (rifabutin + doravirine/doravirine alone) for doravirine $AUC_{0-\infty}$, C_{max}, and C_{24}

Results

Subject disposition

- Eighteen healthy subjects (15 male/3 female) were enrolled and 12 completed the study – subject disposition is summarized in Table 1
  - Six subjects discontinued the study as follows:
    - Five in P2 prior to doravirine administration due to fever with or without other flu-like signs and symptoms
    - One in P1 at the discretion of the principal investigator

Table 1. Subject disposition

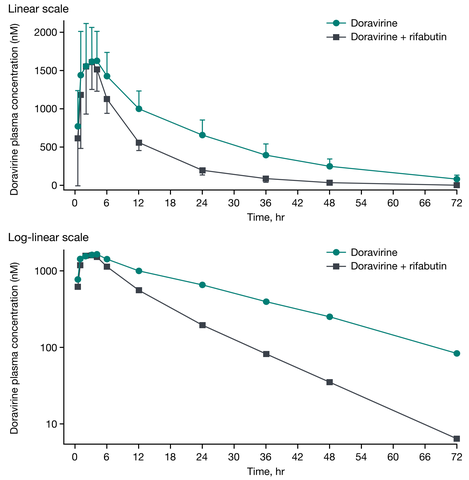
Disposition	
Enrolled, n (%)	18 (100)
Male, n (%)	15 (83.3)
Female, n (%)	3 (16.7)
Age range, years	20–55
Completed, n	12
Discontinued, n	6
Due to AE, n	5 (P2)
Other reason, n	1* (P1)

AE = adverse event
*Investigator decision.

Plasma concentration–time profile of doravirine

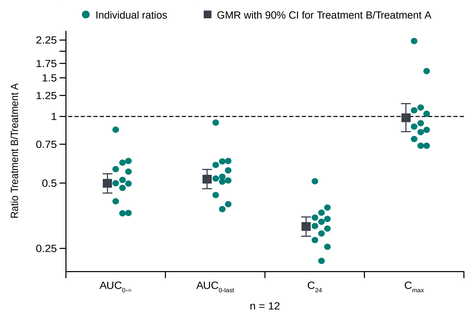
- Doravirine plasma concentration (mean ± standard deviation [SD]) profiles are provided in Figure 2

Figure 2. Doravirine plasma concentration (mean ± SD) profiles following administration of a single oral dose of doravirine 100 mg alone or after rifabutin 300 mg once daily for 14 days to healthy male and female subjects – linear and log-linear scales (limit of quantitation = 2.35 nM)



- Individual ratios, geometric mean ratios (GMRs), and 90% CIs of doravirine + rifabutin/doravirine alone for doravirine plasma PK parameters are plotted in Figure 3

Figure 3. Individual ratios, GMR, and 90% CI for doravirine plasma pharmacokinetic parameters following administration of a single oral dose of 100 mg doravirine alone or after 300 mg rifabutin once daily for 14 days to healthy male and female subjects



A = doravirine treatment; $AUC_{0-\infty}$ = area under the concentration–time curve from time zero to infinity; AUC_{0-last} = AUC from time 0 to time of last quantifiable sample; B = doravirine + rifabutin treatment; C_{24} = concentration at 24 hours post-dose; CI = confidence interval; C_{max} = peak plasma concentration; GMR = geometric mean ratio.

PK of doravirine

- Following co-administration with multiple-dose rifabutin, doravirine C_{max} was not affected; however, $AUC_{0-\infty}$ and C_{24} values were reduced by approximately 50% and 68%, respectively (Table 2)

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

Pharmacokinetic Parameter	Doravirine + Rifabutin (n = 12)	Doravirine (n = 18)	Doravirine + Rifabutin/Doravirine	
	GM (95% CI)		GMR (90% CI)	Intra-subject CV%†
$AUC_{0-\infty}$, hr·μM‡	19.7 (17.7, 21.8)	39.5 (34.3, 45.5)	0.50 (0.45, 0.55)	16.0
AUC_{0-last}, hr·μM‡	19.5 (17.5, 21.7)	37.5 (32.8, 42.8)	0.52 (0.47, 0.58)	15.6
C_{max} (nM)‡	1730 (1470, 2030)	1740 (1560, 1950)	0.99 (0.85, 1.15)	21.8
C_{24} (nM)‡	197 (169, 230)	625 (530, 737)	0.32 (0.28, 0.35)	14.6
T_{max}, hr, median (range)	2.50 (0.50, 4.00)	3.00 (1.00, 6.00)	NA	
$t_{½}$ (hr), GM (CV%)*	9.39 (17.0)	15.7 (18.0)	NA	
CL/F (L/hr), GM (CV%)*	12.2 (18.8)	5.94 (29.0)	NA	
V_d/F (L), GM (CV%)*	166 (27.7)	134 (26.6)	NA	

√ = square root; $AUC_{0-\infty}$ = area under the concentration–time curve from time zero to infinity; AUC_{0-last} = AUC from time 0 to time of last quantifiable sample; C_{24} = concentration at 24 hours post-dose; CI = confidence interval; CL/F = apparent clearance; C_{max} = peak plasma concentration; CV = coefficient of variation; GM = geometric mean; GMR = geometric least-squares mean ratio between-treatments; hr = hour; $t_{½}$ = apparent terminal half-life; T_{max} = time to peak plasma concentration; V_d/F = apparent volume of distribution during the terminal phase after dosing.
†Estimated based on the elements of the variance-covariance matrix as: CV(%)=100*√[(nA²+σB² – 2*σAB)/2].
‡Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
Statistics for $t_{½}$, CL/F, and Vd/F: GM and CV% = 100√(exp(s²)-1), where s^2 is the observed between-subjects variance on the natural log-scale; exp = exponential function.

- Considering the large amount of missing data (6 out of 18 subjects) for doravirine 100 mg + rifabutin 300 mg once daily, an additional statistical analysis was performed including only subjects who completed the study – the results are consistent between the full data set and the subset after excluding subjects who did not complete the study

Safety

- Administration of doravirine and rifabutin was generally well tolerated in healthy subjects:
  - There were no serious AEs
  - Overall, 70 AEs were reported by 17 study subjects; most were mild in intensity
  - At least 1 AE was experienced by 3 (16.7%) and 16 (94.1%) subjects in P1 (doravirine alone) and P2 (doravirine + rifabutin), respectively
    - In P1, none of the AEs were considered treatment-related
    - Most AEs (41/65) in P2 occurred prior to treatment with doravirine and were considered related to rifabutin treatment
    - No more than one subject experienced any specific AE in P1
    - In P2, most common AEs, n (%) were headache, 8 (47.1); fever, 7 (41.2); and chromaturia, 6 (35.3)
    - Drug-related AEs reported during P1 and P2 are presented in Table 3

Discussion

- The reduction observed in doravirine AUC is consistent with the inductive effect of rifabutin on CYP3A4
  - The inductive effect of rifabutin is also reflected in the increased CL/F of doravirine in the presence of rifabutin (12.2 L/hr compared with 5.94 L/hr when administered alone) – as expected for a moderate inducer, this effect was not as large as that observed for rifampin
  - Consistent with increased CL/F, the $t_{½}$ of doravirine was shortened from 15.7 hours to 9.4 hours after co-administration with rifabutin
- Following concomitant administration of rifabutin, doravirine C_{24} exceeded the PK target (78 nM) based on efficacy against the wild-type virus from in vitro studies (data on file)
- Furthermore, based on inter-subject variability in C_{24} 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[7]

Table 3. Incidence of drug-related adverse events

	P1 Doravirine (N=18)	P2 Rifabutin + Doravirine (N=17)	Total (N = 18)
	n (%)		
Subjects with >1 drug-related AE*	0 (0)	14 (82.4)	14 (77.8)
Subjects with no AEs/no drug-related AEs	18 (100.0)	3 (17.6)	4 (22.2)
MedDRA preferred term	n, (%)		
Lymphopenia	0 (0)	3 (17.6)	3 (16.7)
Palpitations	0 (0)	1 (5.9)	1 (5.6)
Tachycardia	0 (0)	2 (11.8)	2 (11.1)
Abdominal pain upper	0 (0)	1 (5.9)	1 (5.6)
Diarrhea	0 (0)	1 (5.9)	1 (5.6)
Flatulence	0 (0)	1 (5.9)	1 (5.6)
Chills	0 (0)	3 (17.6)	3 (16.7)
Pyrexia	0 (0)	7 (41.2)	7 (38.9)
Blood urine present	0 (0)	1 (5.9)	1 (5.6)
Eosinophil count decreased	0 (0)	1 (5.9)	1 (5.6)
Monocyte count decreased	0 (0)	1 (5.9)	1 (5.6)
Neutrophil count decreased	0 (0)	1 (5.9)	1 (5.6)
White blood cell count decreased	0 (0)	1 (5.9)	1 (5.6)
Headache	0 (0)	7 (41.2)	7 (38.9)
Chromaturia	0 (0)	6 (35.3)	6 (33.3)
Tachypnea	0 (0)	1 (5.9)	1 (5.6)
Rash	0 (0)	1 (5.9)	1 (5.6)
Hypotension	0 (0)	1 (5.9)	1 (5.6)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
*Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once within a category; the same subject may appear in different categories.

Conclusions

- Administration of doravirine alone and after multiple doses of rifabutin was generally well tolerated
- Multiple dosing of rifabutin reduced doravirine $AUC_{0-\infty}$ by 50% and C_{24} by 68% via CYP3A4 induction, as compared with doravirine administered alone. Doravirine C_{max} 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

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Disclosures

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