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Multiple-Dose Treatment With Ritonavir Increases the Exposure of Doravirine

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Introduction

- Doravirine (MK-1439) is a novel, potent, 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 therapies[1]
- Doravirine is primarily metabolized by oxidation via cytochrome P450 (CYP) 3A and, while it is a substrate for P-glycoprotein (P-gp) transport *in vitro*, doravirine pharmacokinetics are unlikely to be affected by P-gp modulators as P-gp does not appear to have a significant role *in vivo*. Furthermore, P-gp efflux may not limit absorption of doravirine due to its high permeability[2]
- Based on preclinical and clinical data, doravirine is unlikely to be a perpetrator of drug–drug interactions[1-3]; however, a potential exists for doravirine to be a victim of drug interactions mediated via CYP3A inhibitors and inducers
- Ritonavir is an HIV-1 protease inhibitor commonly used in highly active antiretroviral therapy and functions as a metabolic boosting agent through CYP3A inhibition[4,5]
- Ritonavir is a mixed metabolic inhibitor and inducer
  - In addition to CYP3A, ritonavir also inhibits P-gp and CYP2D6, while inducing UDP glucuronosyltransferases (UGTs), CYP3A, CYP1A2, and CYP2C9[6,7]
- As doravirine may be administered in combination with ritonavir-boosted protease inhibitors (PIs) as part of highly active antiretroviral therapy, the pharmacokinetics and safety of doravirine following ritonavir administration warrants investigation

Objective

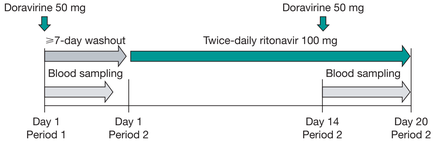
- This study was performed to evaluate the pharmacokinetics, safety, and tolerability of a single dose of doravirine (MK-1439) administered with multiple doses of ritonavir

Methods

Study design

- This was an open-label, fixed-sequence, 2-period study in healthy young men 18–50 years of age (Protocol no.: MK-1439-002; Figure 1)
- The study was performed in accordance with Institutional Review Board/Independent Ethics Committee and International Conference on Harmonisation Good Clinical Practice Guidelines and all subjects provided written informed consent

Figure 1. Study design



Treatment

- In Period 1, subjects received a single oral dose of doravirine 50 mg followed by a washout period of at least 7 days
- In Period 2, twice-daily ritonavir 100 mg was administered for 20 days and on Day 14 doravirine 50 mg was coadministered with the morning dose
- Both doses of doravirine were administered following an overnight fast of at least 8 hours; water was restricted 1 hour prior to, and following, study drug administration. The subjects remained fasted for 4 hours postdose
- With the exception of the Day 14 morning dose, ritonavir was administered within 30 minutes of a meal. The evening dose was administered 10–12 hours after the morning dose

Pharmacokinetic assessments

- Blood samples to determine plasma doravirine pharmacokinetics were collected at predose and over selected time points for 120 hours postdose on Day 1 in Period 1, and predose to 168 hours postdose on Day 14 in Period 2
- Natural-log–transformed pharmacokinetic parameters (area under the curve [AUC] from predose to infinity [$AUC_{0-\infty}$], maximum measured concentration [C_{max}], and concentration 24 hours postdose [C_{24}]) were analyzed using a linear mixed-effects model. The model included treatment as a fixed effect and subject as a random effect
- 90% confidence intervals (CI) of the geometric least-squares means ratios (GMR; doravirine + ritonavir/doravirine alone) and 95% CI for the geometric means of doravirine $AUC_{0-\infty}$, C_{max}, and C_{24} were constructed
- Additionally, time to C_{max} (T_{max}) and apparent terminal half-life ($t_{½}$) were generated from the concentration–time data

Safety

- Safety was assessed throughout the study by adverse event (AE) monitoring, laboratory evaluations, vital signs, physical examination, and electrocardiogram

Results

Study population

- Eight white men with a mean age of 29.4 years (range: 21–46 years) and mean body mass index of 22.1 kg/m^2 (range 17.8–25.1 kg/m^2) were enrolled and completed the study

Plasma concentration–time profiles

- Doravirine plasma concentration–time profiles with and without twice-daily ritonavir are shown in Figure 2

Doravirine pharmacokinetics

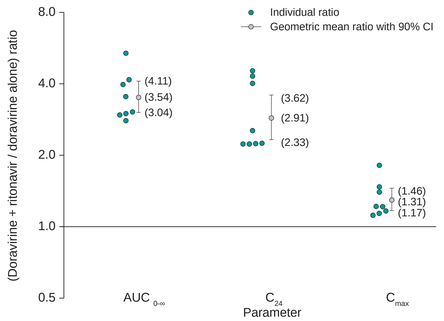
- Doravirine $AUC_{0-\infty}$, C_{max}, and C_{24} were increased in subjects when coadministered with twice-daily ritonavir versus single-dose doravirine alone (Table 1 and Figure 3)
- In addition, both T_{max} and $t_{½}$ were increased when doravirine was administered with twice-daily ritonavir versus without (Table 1)

Table 1. Doravirine plasma pharmacokinetics — summary statistics following administration of a single oral dose of doravirine 50 mg alone or on Day 14 of a 20-day treatment with twice-daily ritonavir 100 mg in healthy subjects

Parameter	Doravirine alone (N=8)	Doravirine + ritonavir (N=8)	Doravirine + ritonavir/ doravirine alone
	GM (95% CI)	GM (95% CI)	GMR (90% CI)
$AUC_{0-\infty}$ (μM•h)†	20.8 (17.5, 24.6)	73.5 (62.0, 87.1)	3.54 (3.04, 4.11)
C_{max} (nM)†	963 (825, 1120)	1260 (1080, 1470)	1.31 (1.17, 1.46)
C_{24} (nM)†	322 (266, 390)	935 (772, 1130)	2.91 (2.33, 3.62)
T_{max} (h)‡	3.50 (2.00, 5.00)	5.00 (1.00, 16.00)	
$t_{½}$ (h)§	13.97 (10.59)	35.16 (12.27)	

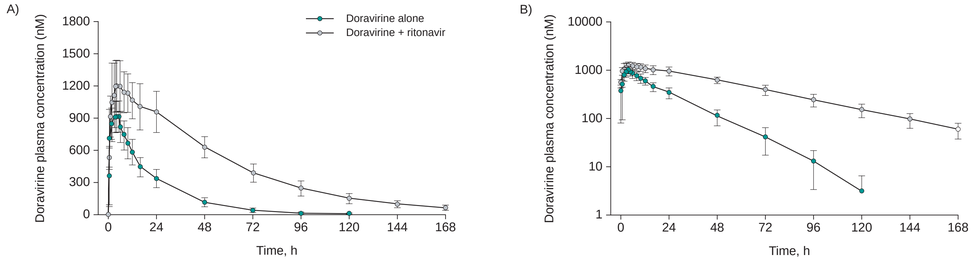
†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural-log–transformed values
‡Median (min, max)
§Geometric mean and percent geometric coefficient of variation
AUC = area under the plasma concentration–time curve; $AUC_{0-\infty}$ = AUC from predose to infinity; C_{24} = concentration 24 hours postdose; CI = confidence interval; C_{max} = maximum measured concentration; GM = geometric mean; GMR = geometric mean ratio; $t_{½}$ = apparent terminal half-life; T_{max} = time to C_{max}

Figure 3. Individual $AUC_{0-\infty}$, C_{max}, and C_{24} doravirine + ritonavir/ doravirine alone ratios and associated GMRs with corresponding 95% CIs following a single oral 50 mg dose of doravirine



$AUC_{0-\infty}$ = area under the plasma concentration–time curve from predose to infinity; C_{24} = concentration 24 hours postdose; C_{max} = maximum measured concentration; CI = confidence interval; GMR = geometric mean ratio

Figure 2. Plasma concentration–time profiles of doravirine following a single oral 50 mg dose of doravirine alone and with ritonavir in healthy subjects — A) linear (mean ± standard deviation) and B) log-linear scales



Safety

- Administration of single-dose doravirine 50 mg with and without twice-daily ritonavir 100 mg was generally well tolerated by the healthy subjects
  - All subjects reported one or more AEs; a total of 22 AEs occurred during the study
  - All AEs were mild, with the exception of one headache of moderate intensity deemed to be unrelated to the study treatments
  - In total, 5 subjects reported 11 AEs that were deemed to be treatment related (Table 2)
  - The only AE to be reported by more than one subject was headache (n=3, 37.5%)
  - No subject experienced serious AEs or discontinued due to AEs

Table 2. Incidence of treatment-related adverse events

	Doravirine alone	Ritonavir	Doravirine + ritonavir
Subjects with ⩾1 treatment-related AE	0	4 (50.0%)	2 (25.0%)
MedDRA Preferred Term	**n (%)**		
Palpitations	0	1 (12.5%)	0
Abdominal pain	0	1 (12.5%)	0
Flatulence	0	1† (12.5%)	0
Sensation of foreign body	0	1 (12.5%)	0
Headache	0	1 (12.5%)	1 (12.5%)
Somnolence	0	1† (12.5%)	0
Insomnia	0	0	1 (12.5%)

†The same subject reported 3 instances of flatulence (Period 2; Days 2, 9, and 12) and 2 instances of somnolence (Period 2; Days 11 and 12) to take the total number of instances of treatment-related AEs to 11
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities, version 14.1

Discussion

- Coadministration of single-dose doravirine 50 mg with twice-daily ritonavir 100 mg increased exposure to doravirine and prolonged the half-life of doravirine versus doravirine alone
- The increase in doravirine exposure with, versus without, concomitant ritonavir is consistent with ritonavir inhibiting the CYP3A pathway for doravirine metabolism
- Ritonavir also inhibits the P-gp–mediated transport of molecular entities. However, P-gp is not anticipated to play a significant role in limiting doravirine bioavailability as doravirine has high permeability. Thus, inhibition of P-gp is likely to result in small, not clinically relevant increases in absorption
- The magnitude of the ritonavir effect on doravirine was moderate (⩾2-fold, but <5-fold, increase in AUC), despite ritonavir being categorized as a strong CYP3A inhibitor.[8] A reason for this smaller than expected effect may be the low intrinsic clearance of doravirine. In addition, ritonavir may have inductive effects on CYP3A following multiple dosing, which could result in net moderate inhibition[9]
- Doravirine does not meaningfully inhibit or induce CYP3A; therefore, doravirine is not anticipated to have an effect on ritonavir pharmacokinetics[2]

Conclusions

- Multiple doses of twice-daily ritonavir increased single-dose doravirine $AUC_{0-\infty}$, C_{max}, and C_{24} by approximately 3.5-fold, 1.3-fold, and 2.9-fold, respectively, versus doravirine alone
- The absorption of doravirine did not seem to be meaningfully altered by twice-daily ritonavir, despite ritonavir inhibiting P-gp
- Single-dose doravirine administered alone or with multiple doses of ritonavir is generally well tolerated

References

1. Anderson MS et al. Antivir Ther 2015;20:397-405.
2. Sanchez RI et al. Drug Metab Rev 2016;48:73.
3. Khalilieh S et al. Antimicrob Agents Chemother 2016. [Epub ahead of print].
4. Department of Health and Human Services (DHHS). 2016. http://aidsinfo.nih.gov/guidelines. Accessed January 15, 2017.
5. Zeldin RK, Petruschke RA. J Antimicrob Chemother 2004;53:4-9.
6. de Maat MM et al. Clin Pharmacokinet 2003;42:223-282.
7. Drewe J et al. Biochem Pharmacol 1999;57:1147-1152.
8. U.S. Food and Drug Administration (FDA). 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Accessed January 15, 2017.
9. Hsu A et al. Antimicrob Agents Chemother 1997;41:898-905.

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Disclosures

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