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ORIGINAL RESEARCH ARTICLE

A Two-Way Steady-State Pharmacokinetic Interaction Study of Doravirine (MK-1439) and Dolutegravir

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Abstract

Introduction Doravirine, a non-nucleoside reverse-transcriptase inhibitor in development for the treatment of patients with human immunodeficiency virus-1 infection, has potential to be used concomitantly in antiretroviral therapy with dolutegravir, an integrase strand transfer inhibitor. The pharmacokinetic interactions between these drugs were therefore assessed.

Methods Oral formulations of doravirine and dolutegravir were dosed both individually and concomitantly once daily in healthy adults. Twelve subjects (six were male), 23–42 years of age, were enrolled and 11 completed this phase I, open-label, three-period, fixed-sequence study per protocol; one subject was discontinued for a positive cotinine test at admission to period 2. In period 1, dolutegravir 50 mg was administered for 7 days. After a 7-day washout, doravirine 200 mg was dosed for 7 days in period 2, followed (without washout) by both doravirine and dolutegravir simultaneously for 7 days in period 3. Plasma samples were taken to determine dolutegravir and doravirine concentrations.

Results The steady-state concentration 24 h post-dose (C_{24}) of dolutegravir was not substantially altered by co-administration of doravirine multiple doses; area under the plasma concentration–time curve from dosing to 24 h post-dose ($AUC_{0–24}$), maximum concentration (C_{max}), and C_{24} geometric mean ratios were 1.36, 1.43, and 1.27, respectively. The pharmacokinetics of doravirine was not affected by multiple doses of dolutegravir (geometric mean ratios: 1.00, 0.98, and 1.06 for $AUC_{0–24}$, C_{24}, and C_{max}, respectively). Both drugs were generally well tolerated.

Conclusion The results of this study demonstrate that concomitant administration of doravirine and dolutegravir in healthy subjects causes no clinically significant alteration in the pharmacokinetic and safety profiles of the two drugs, thereby supporting further evaluation of co-administration of these agents for human immunodeficiency virus-1 treatment.

Key Points

Concomitant administration of doravirine and dolutegravir in healthy subjects causes no clinically significant alteration in the pharmacokinetic and safety profiles of the two drugs.

Further evaluation of co-administration of these agents for human immunodeficiency virus-1 treatment is supported.

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1 Introduction

Current standard-of-care treatment regimens for the control of human immunodeficiency virus-1 (HIV-1) infection involve two nucleoside analog reverse-transcriptase inhibitors (NRTIs) in combination with either a single non-nucleoside reverse-transcriptase inhibitor (NNRTI), an integrase strand

transfer inhibitor (INSTI), or a pharmacokinetically enhanced protease inhibitor regimen [1]. However, NRTI-based therapy is associated with a broad range of adverse events (AEs) including hyperlactatemia and lactic acidosis, neuropathy, pancreatitis, osteoporosis, kidney deficiency, and lipoatrophy [2–5]. Furthermore, approved NNRTIs and protease inhibitors are also associated with significant AEs [6]. The complexity of treatment regimens, daily pill burdens, and the AE profiles of existing antiretroviral therapies are significant determinants of patient adherence and have a causal link with the emergence of resistance and virologic failure [7]. Subsequently, the simplification of antiretroviral therapy is associated with improved patient convenience, adherence, quality of life, and therapeutic efficacy [8, 9]. Furthermore, the elimination of NRTIs from treatment in favor of co-administered better tolerated regimens with a decreased pill burden in the future is desirable.

Dolutegravir is a once-daily (QD) HIV-1 medication from the INSTI class of drugs [10, 11]. In addition, dolutegravir requires no pharmacokinetic (PK) booster and—based on clinical and in vitro data—has excellent antiviral activity and tolerability, which is typically associated with an INSTI, and also a particularly high barrier to resistance [12–14]. Furthermore, with optimized background therapy, dolutegravir has the potential to provide significant benefit to most adults with multi-drug resistance, which includes resistance to the currently marketed INSTIs. These findings have led to dolutegravir twice daily being approved for use by the US Food and Drug Administration in 2013 and the European Commission in 2014.

Therefore, dolutegravir represents an effective therapy option that can be used in combination with novel compounds from other drug classes that are in development to supersede current treatment regimens. One such candidate to replace NRTIs in a concomitant treatment with dolutegravir is doravirine (MK-1439), a novel NNRTI currently in clinical development [15] that has demonstrated efficacy against HIV-1 (including NNRTI-resistant mutants) and a favorable safety profile in phase II trials [16, 17]. In one such phase II study, the tolerability and efficacy of doravirine at doses ranging from 25 to 200 mg QD in combination with tenofovir disoproxil and emtricitabine was clearly demonstrated in antiretroviral therapy-naïve patients with HIV-1 infection [18]. In the same study, the doravirine-based regimen was associated with fewer treatment-emergent, central nervous system AEs in comparison with an existing NNRTI, efavirenz 600 mg, also in combination with tenofovir disoproxil and emtricitabine. These positive results have led to the evaluation of doravirine at the 100-mg dose in ongoing phase III trials.

The individual efficacies of both doravirine and dolutegravir suggest that concomitant administration in a compact NRTI-sparing regimen could be an attractive, albeit currently untested, therapy option. The potential of this co-therapy is further supported through the limited potential of both compounds to be perpetrators or victims of drug–drug interactions and the favorable tolerability of each individual product in separate studies [15, 19, 20]; however, that these agents will exhibit a similar safety profile when co-administered has yet to be demonstrated. The present study aimed to evaluate the two-way PK interaction of doravirine and dolutegravir under steady-state conditions and to examine the safety and tolerability of doravirine and dolutegravir when co-administered to steady state in healthy subjects.

In this study, subjects were dosed with doravirine 200 mg under fasted conditions. The rationale for this dose was that doravirine 200 mg was the highest dose proposed for pivotal trials at the time of designing this study and demonstrated a favorable tolerability profile in a prior dose-ranging study [18]. The fasted state was maintained for dosing to allow comparison with earlier trials and to minimize PK variability.

2 Material and Methods

The study described here was a phase I, open-label, three-period, fixed-sequence study designed to evaluate the steady-state pharmacokinetics, safety, and tolerability of doravirine alone and in combination with dolutegravir in healthy subjects (Merck protocol 1439-016). This single-center clinical study was conducted at the PAREXEL International Early Phase Clinical Unit in Baltimore Harbor Hospital, Baltimore, MD, USA. Informed consent was obtained from all individual participants included in the study. In addition, the study was approved by the Aspire Institutional Review Board and performed according to Good Clinical Practice Guidelines and in accordance with the ethical standards as laid down in the Declaration of Helsinki.

The primary objectives of the study were to assess the effect of doravirine at steady state on the plasma pharmacokinetics of dolutegravir and to assess the effect of dolutegravir at steady state on the pharmacokinetics of doravirine. The secondary objectives of the study were the safety and tolerability of concomitant doravirine and dolutegravir administration. Study endpoints were the PK characteristics and safety data for both doravirine and dolutegravir under steady-state conditions.

2.1 Study Population and Procedures

This study enrolled non-smoking (for $\geq$6 months), healthy adults between the ages of 18 and 45 years with a body mass index of $\geq$18.5 to $\leq$32.0 kg/m^2 (minimum weight $\geq$50 kg) at the screening visit. Key exclusion criteria included subjects having an estimated creatinine clearance

of ≤80 mL/min, based on the Cockcroft–Gault equation, and blood samples or previous exposure or hypersensitivity to the drugs used in the study.

A fixed-sequence design was used to minimize the time required to assess study subjects, and to eliminate the need for an additional washout interval that would be needed to resolve any potential inductive effects of either drug, however small.

In period 1 of the study, subjects received oral dolutegravir 50 mg QD for 7 days. This was followed by a 7-day washout interval before period 2 in which doravirine 200 mg was administered orally, QD for 7 days. Both dolutegravir 50 mg and doravirine 200 mg were then administered simultaneously in period 3 for 7 days. There was no washout interval between periods 2 and 3. In each of periods 1, 2, and 3, a standardized meal (including breakfast approximately 1 h after dosing) was served on days 1–6. However, to reduce PK variability during intensive PK sampling, the trial drugs were administered without food on day 7 of each period following an overnight 10-h fast. Plasma samples for PK analyses of both doravirine and dolutegravir were collected pre-dose on days 5 and 6 and at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 7, 12, and 24 h post-dose on day 7 in each test period. Drug concentrations in the plasma samples were determined using validated, reversed-phase ultra-performance liquid chromatography with tandem mass spectrometric detection. The lower limit of quantification using this technique was 1 ng/mL and the detection range was between 1 and 16,000 ng/mL.

2.2 Pharmacokinetic Evaluations

The PK parameters of area under the plasma concentration–time curve from dosing to 24 h post-dose (AUC_{0-24}), maximum concentration (C_{max}), time corresponding to occurrence of C_{max}, and concentration at 24 h post-dose (C_{24}) of dolutegravir and doravirine individually and when co-administered to steady state were analyzed for all subjects. These parameters were derived using non-compartmental analysis methods from the concentration–time data using Phoenix® WinNonlin® Professional (version 6.3 or higher). Specifically, the AUC_{0-24} was calculated using the "linear up, log down" calculation method option in WinNonlin® (Certara USA, Inc., Princeton, NJ).

2.3 Safety Assessments

Throughout the study, measurements of vital signs by electrocardiogram, physical examination, and laboratory safety tests were performed. In addition, any AEs were catalogued, graded in intensity, and monitored.

2.4 Data Analysis and Statistics

For both doravirine and dolutegravir, trough concentrations (C_{24}) are associated with antiretroviral activity and were selected as an endpoint by which to judge the extent of the interaction on either drug relative to the lower bound associated with efficacy. Based on dolutegravir monotherapy studies and dose-ranging trials, a decrease of >75 % in C_{24} was assigned for the lower dolutegravir clinical significance bound. Doravirine safety and efficacy bounds are not yet fully defined. However, based on doravirine antiretroviral effects from a prior monotherapy study in HIV-1-infected individuals [21], a lower bound of 0.5 for the limit of change in C_{24} was assigned for the lower doravirine clinical significance bound. With respect to increased exposures, no studied dolutegravir exposure has been associated with increased AEs or toxicity. Thus, no specific upper area under the plasma concentration–time curve (AUC) safety bound was employed for dolutegravir. Similarly, while no studied doravirine exposure has been associated with specific safety findings, a relatively conservative upper safety bound of 2.0 for AUC was assigned for this investigational medicine.

Sample size was calculated by assessing the statistical power associated with dolutegravir and doravirine C_{24} and doravirine AUC_{0-24}. Assuming the within-subject standard deviation estimate (on the natural log scale) of 0.322 for dolutegravir C_{24}, 0.167 for doravirine AUC_{0-24}, and 0.199 for doravirine C_{24}, ten subjects completed, nonnegative correlation among dolutegravir and doravirine C_{24} and doravirine AUC_{0-24}, and true geometric least-squares mean ratios (GMRs) of 1.00 for all parameters, there would be at a 99.7 % probability that the lower limit of the 90 % confidence interval (CI) of dolutegravir C_{24} is >0.25, the upper limit of the 90 % CI of doravirine AUC_{0-24} is <2.0, and the lower limit of the 90 % CI of doravirine C_{24} is >0.5 simultaneously. Therefore, to allow for dropouts, the sample size was set at 12 subjects.

The AUC_{0-24}, C_{max}, and C_{24} for both doravirine and dolutegravir were natural log transformed prior to analysis and evaluated separately using a linear mixed-effects model with fixed-effects term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED (Statistical Analysis Software Version 9.2; SAS® Institute Inc., Cary, NC, USA). The Kenward–Roger method was used to calculate the denominator degrees of freedom for the fixed effects [22]. In addition, 90 % CIs for the GMRs were obtained from the above model (dolutegravir + doravirine/dolutegravir alone and dolutegravir + doravirine/doravirine alone). The steady-state plasma C_{24} for

dolutegravir by doravirine was not considered clinically significant if the lower limit of the 90 % CI of dolutegravir C_{24} GMR (dolutegravir + doravirine/dolutegravir alone) is >0.25. Steady-state plasma AUC_{0-24} and C_{24} for doravirine was considered unaltered by dolutegravir if the upper limit of the 90 % CI of doravirine AUC_{0-24} GMR (dolutegravir + doravirine/doravirine alone) is <2.0 and the lower limit of the 90 % CI of doravirine AUC_{0-24} GMR (dolutegravir + doravirine/doravirine alone) is >0.5.

3 Results

3.1 Study Population

Of the 12 subjects enrolled between October and December 2013, six were male and 11 completed the study as per protocol; one male subject discontinued after 7 days, and after completing the dolutegravir dosing period, at the principal investigator's discretion owing to a positive cotinine test. The mean age of the enrolled subjects was 32.5 years (range 23–42 years) and the mean body mass index was 28.15 kg/m^2 (range 21.6–31.8 kg/m^2). Three subjects were categorized as Hispanic or Latino, eight were Black or African-American, and four were White.

3.2 Plasma Pharmacokinetics of Dolutegravir

The mean dolutegravir plasma concentration–time profiles, with and without co-administration of doravirine, are shown in Fig. 1 and the PK values are shown in Table 1. The steady-state plasma C_{24} of dolutegravir was not substantially altered by the co-administration of doravirine according to the pre-specified bounds for clinical significance. Dolutegravir steady-state AUC_{0-24}, C_{max}, and C_{24} were increased after co-administration with doravirine, while time corresponding to occurrence of C_{max} remained unchanged. The GMRs for dolutegravir + doravirine/dolutegravir alone AUC_{0-24}, C_{max}, and C_{24} can be seen in Fig. 2a. The trough concentrations of dolutegravir for days 5–8 in the presence and absence of co-administered

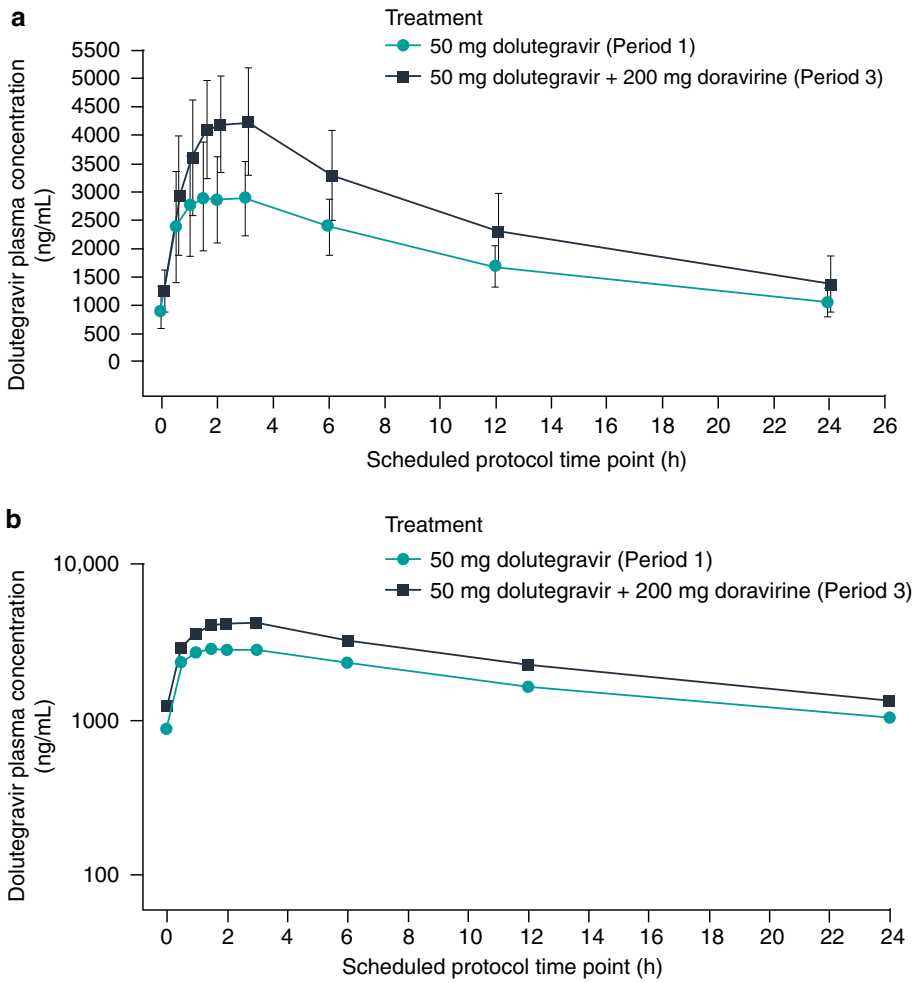

Fig. 1 Arithmetic mean steady-state dolutegravir plasma concentration profile with and without co-administration with doravirine: **a** linear scale (±SD) and **b** semi-log scale. *SD* standard deviation

Table 1 Steady-state pharmacokinetic parameters and treatment comparison for dolutegravir (50 mg QD) and doravirine (200 mg QD)

Dolutegravir parameter	Dolutegravir alone			Dolutegravir + doravirine			Dolutegravir + doravirine/dolutegravir alone	
	N	GM	95 % CI	*N*	GM	95 % CI	GMR	90 % CI
$AUC_{0–24}$ (h·ng/mL)	12	42,900	(37,000, 49,600)	11	58,500	(48,600, 70,500)	1.36	(1.15, 1.62)
C_{24} (ng/mL)	12	1010	(844, 1220)	11	1290	(1010, 1650)	1.27	(1.06, 1.53)
C_{max} (ng/mL)	12	3070	(2590, 3640)	11	4400	(3810, 5070)	1.43	(1.20, 1.71)
T_{max} (h)[a]	12	1.50	(0.50, 3.02)	11	1.50	(1.00, 3.00)	–	–
Doravirine parameter	Doravirine alone			Dolutegravir + doravirine			Dolutegravir + doravirine/doravirine alone	
	N	GM	95 % CI	*N*	GM	95 % CI	GMR	90 % CI
$AUC_{0–24}$ (μM·h)	11	47.6	(40.1, 56.4)	11	47.6	(39.7, 57.1)	1.00	(0.89, 1.12)
C_{24} (nM)	11	993	(797, 1240)	11	975	(753, 1260)	0.98	(0.88, 1.09)
C_{max} (nM)	11	3540	(2900, 4330)	11	3760	(3080, 4590)	1.06	(0.88, 1.28)
T_{max} (h)[a]	11	1.50	(0.52, 3.02)	11	2.00	(0.50, 3.00)	–	–

$AUC_{0–24}$ area under the plasma concentration–time curve from dosing to 24 h post-doseover the dosing interval, *C_{24}* plasma concentration at 24 h post-doseours, *CI* confidence interval, *C_{max}* maximum plasma plasma concentration, *GM* geometric mean, *GMR* geometric mean ratio, *N* number of subjects exposed to each treatment, *PK* pharmacokinetic, *QD* once daily, *T_{max}* time to maximum plasma concentration

[a] Reports the median value, minimum, and maximum

doravirine are shown in Table 2. The trough concentrations were similar across days 5–8, consistent with the achievement of steady-state conditions.

3.3 Plasma Pharmacokinetics of Doravirine

The mean doravirine plasma concentration–time profiles, with and without co-administration of dolutegravir, are shown in Fig. 3 and the PK parameter values are shown in Table 1. Steady-state $AUC_{0–24}$, C_{max}, and C_{24} of doravirine were unchanged by co-administration with dolutegravir. The GMRs for dolutegravir + doravirine/doravirine alone $AUC_{0–24}$, C_{max}, and C_{24} can be seen in Fig. 2b. The trough concentrations of doravirine for days 5–8 in the presence and absence of co-administered dolutegravir are shown in Table 2. As observed for dolutegravir, trough concentrations were similar across days 5–8, consistent with the achievement of steady-state conditions.

3.4 Safety

Both doravirine and dolutegravir were generally well tolerated, with no severe clinical or laboratory AEs reported. No subject discontinued from the study because of an AE. In total, the following five AEs were reported by four subjects; two AEs in period 1 (constipation and myalgia), two in period 2 (conjunctivitis and musculoskeletal stiffness), and a single AE in period 3 (constipation). All reported AEs were mild in intensity and were not considered to be related to treatment. No clinically meaningful changes were observed for vital signs, electrocardiogram, or other clinical parameters assessed.

4 Discussion

This study was designed as an open-label, three-period, fixed-sequence study to evaluate the steady-state pharmacokinetics and safety and tolerability of the multiple-dose administration of doravirine or dolutegravir, both alone and co-administered, in healthy male and female subjects. To fully assess the potential for interaction between these drugs, doses of 50 mg dolutegravir, the clinically recommended dose and 200 mg doravirine, the highest dose explored in a phase IIb study [18], were selected for this study. The results of this study demonstrate that the co-administration of doravirine and dolutegravir does not cause clinically meaningful changes in the PK profiles of either agent, as judged by the relatively small changes observed in C_{24} and in AUC relative to the efficacy and safety margins defined through prior study (discussed in Sect. 2.3). Under steady-state conditions, daily dolutegravir 50 mg—the suggested dose for integrase-naïve patients—did not substantially alter doravirine pharmacokinetics ($AUC_{0–24}$ and C_{24}) as compared with doravirine administered alone. This lack of change in C_{24} is of clinical importance given the association between maintenance optimal drug concentrations and antiretroviral activity [23]. Doravirine has been demonstrated to maintain efficacy at trough concentrations of 107 nM and has a predicted projected efficacy threshold of 78 nM based on in vitro results [24, 25], both of which were exceeded in the current study by approximately tenfold. Furthermore, as per the dolutegravir prescribing information, dolutegravir may be administered without regard to meals, even though co-administration with a high-fat meal increased mean C_{max} and

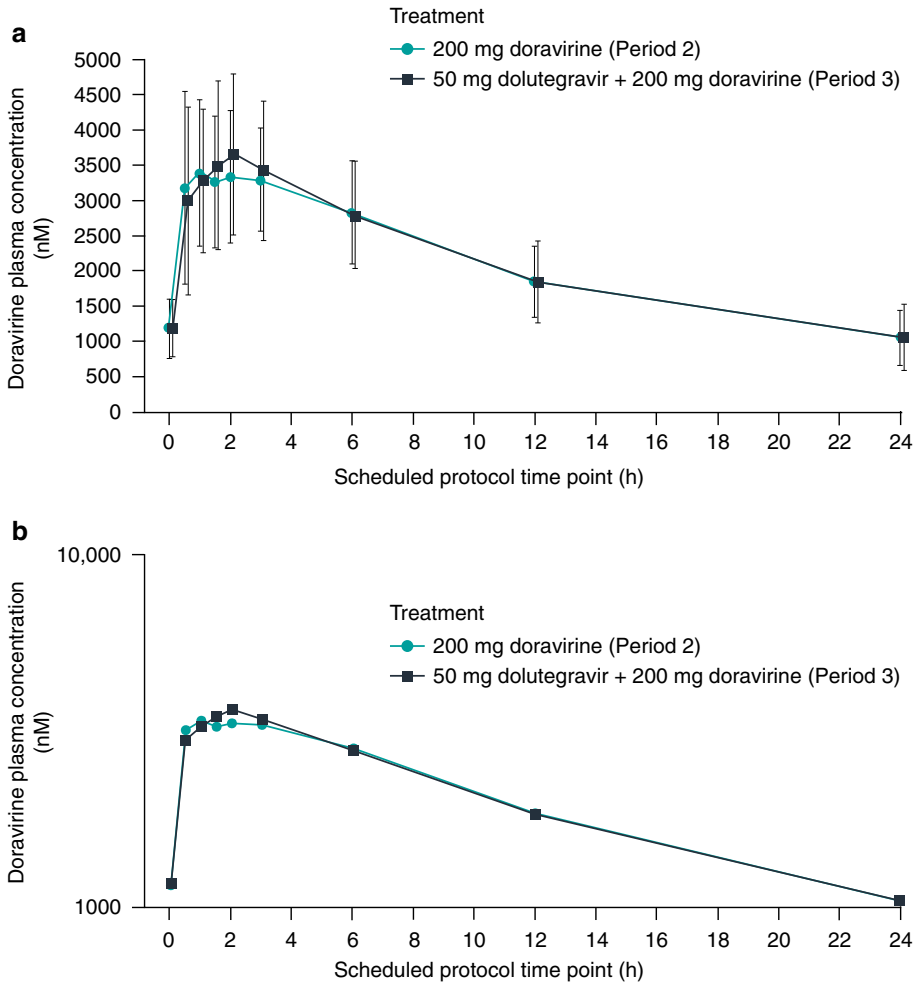

Fig. 2 Individual analyte parameter ratios for dolutegravir (**a**) and doravirine (**b**) with geometric mean ratios and 90 % confidence intervals following multiple-dose administration with and without the additional treatment [doravirine and dolutegravir, respectively (per-protocol population)]. AUC_{0-24} area under the plasma concentration–time curve from dosing to 24 h post-dose, C_{24} concentration 24 h post-dose, C_{max} maximum concentration

Table 2 Mean trough concentrations for doravirine and dolutegravir on days 5–8

Analyte	Treatment	Mean trough concentration (±standard deviation)			
		Day 5	Day 6	Day 7	Day 8
Dolutegravir (ng/mL)	Dolutegravir alone (period 1)	935 (±315)	870 (±287)	909 (±319)	1050 (±258)
	Dolutegravir + doravirine (period 3)	1210 (±446)	1230 (±462)	1250 (±369)	1370 (±494)
Doravirine (nM)	Doravirine alone (period 2)	1300 (±391)	1300 (±262)	1170 (±426)	1050 (±388)
	Doravirine + dolutegravir (period 3)	1260 (±552)	1180 (±359)	1180 (±406)	1050 (±471)

AUC by approximately 66 % [26, 27], an increase greater than that observed in this study. Therefore, the increases in dolutegravir exposure observed in the present study are within established safety margins and are not considered clinically meaningful [26, 27]. The effect of doravirine on the higher dose of 50 mg twice daily for patients with integrase-resistant HIV remains to be seen. However, because the dose of doravirine being evaluated in phase III trials is lower (100 mg) than the 200 mg evaluated in this study, the observed effects on dolutegravir can be expected to be further decreased at the clinical dose of doravirine.

The lack of clinically meaningful interactions between doravirine and dolutegravir can be rationalized by considering the specific metabolic pathways of each drug. Dolutegravir is metabolized primarily by uridine 5′-diphospho-glucuronosyltransferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A4 and is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro [28]. Based on in vitro data and the results of a clinical trial with midazolam, doravirine is not expected to be an inhibitor of UGT1A1, CYP3A4, or P-gp [15, 20]. In vitro, doravirine

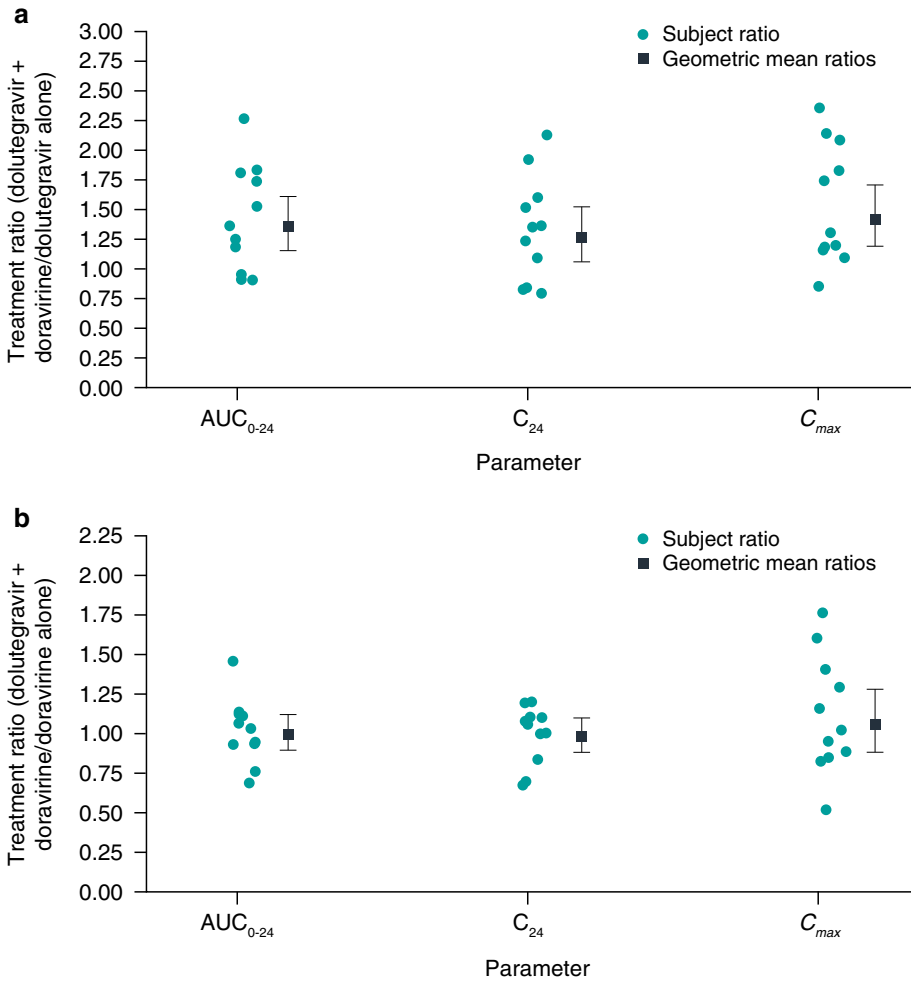

Fig. 3 Arithmetic mean steady-state doravirine plasma concentration profile with and without co-administration with dolutegravir: **a** linear scale (±SD) and **b** semi-log scale. *SD* standard deviation

inhibits BCRP with a half maximal inhibitory concentration (IC_{50}) value of 51 μM, which is well above the plasma C_{max} value of doravirine (<4 μM); therefore, inhibition of BCRP at the systemic level is not anticipated [20]. There is, however, potential for inhibition of BCRP at the gut level that may explain the modest increases in dolutegravir exposure observed in this study. The modest increase in steady-state dolutegravir exposure ($AUC_{0–24}$, C_{max}, and C_{24}) by the co-administration of doravirine (200 mg QD) observed in the current trial was not considered clinically significant given the safety/tolerability profile of dolutegravir and the accumulated exposure–antiviral response relationship [29–31]. In previous trials, other NNRTIs, including etravirine and nevirapine, have been shown to decrease exposure to dolutegravir [32, 33]. Therefore, the increased exposure to dolutegravir observed in this study, in combination with the good tolerability of dolutegravir [34], suggest that doravirine may confer an advantage in comparison with other NNRTIs when co-administered with dolutegravir.

In the reverse comparison during this study, dolutegravir had little discernible effect on doravirine pharmacokinetics, which was expected given existing knowledge of both treatments. Doravirine is primarily metabolized by CYP3A4 [20] and, in earlier studies, dolutegravir was demonstrated to have a low potential for inducing or inhibiting CYP enzymes both in vitro and in healthy individuals [28, 35]. Furthermore, doravirine is known to be a substrate for P-gp [20] and, although dolutegravir shares this characteristic, no induction or inhibition effects have been observed associated with the latter in vitro [28].

In addition to the favorable PK results, multiple doses of doravirine in combination with dolutegravir were generally well tolerated in healthy subjects. This reflects the safety and tolerability profiles associated with each drug separately, as reported in previous clinical trials [18, 36].

The relevant potential limitations of this study concern the restricted duration of dosing in healthy subjects relative to long-term dosing of HIV-1-infected subjects harboring a variety of co-morbid conditions as managed in clinical practice. The doravirine 200-mg dose was selected at the time of designing this study as the highest dose with

reasonable potential for use in later pivotal trials. Since this trial was conducted, doravirine 100 mg was selected as the clinically intended dose. Therefore, the interactions reported in the current study can be considered to be greater than what will be expected in the clinic.

The observed lack of interaction between doravirine and dolutegravir and the favorable tolerability profile of the two agents when co-administered has implications from a therapeutic perspective. The current standard of care for antiretroviral therapy is the use of combination therapies consisting of an anchor therapy, such as an NNRTI or an INSTI, with a backbone of two NRTIs. In an NRTI-sparing regimen, doravirine may ultimately provide a viable alternative to the less well-tolerated NRTIs when combined with other favorable therapies, such as dolutegravir, as seen in this study. Furthermore, the doravirine–dolutegravir combination may represent a suitable second-line or salvage therapy for patients with infections resistant to NRTIs. Both of these proposed treatments are surplus to the initial indication for doravirine development, but results to date suggest that these may represent a viable and beneficial option. However, the safety and efficacy of such a combination in patients with HIV remain to be evaluated in clinical study.

5 Conclusions

In this study, co-administration of doravirine 200 mg under steady-state conditions after QD dosing did not have a clinically meaningful effect on the pharmacokinetics of dolutegravir 50 mg compared with that of dolutegravir 50 mg alone. Furthermore, under steady-state conditions, the co-administration of dolutegravir 50 mg did not affect the pharmacokinetics of doravirine 200 mg compared with the administration of doravirine 200 mg alone. Co-administration of multiple doses of doravirine 200 mg and dolutegravir 50 mg was generally well tolerated. Therefore, the PK results and safety profiles of doravirine 200 mg and dolutegravir 50 mg support the concomitant administration of the intended clinical dose of doravirine 100 mg, with dolutegravir 50 mg without dose adjustment as part of an antiretroviral therapy regimen.

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Compliance with Ethical Standards

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Conflict of interest MSA, SK, KLY, RL, LF, MLR, VS, and JRB are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options. AH has nothing to disclose. IS was an employee of GlaxoSmithKline, Research Triangle Park, NC, USA at the time of the study. LLR and AMB are current employees of ViiV Healthcare, Research Triangle Park, NC, USA.

Informed consent Informed consent was obtained from all individual participants included in the study.

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