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Pharmacokinetic interaction between single and multiple doses of darunavir, in combination with cobicistat or ritonavir, and single-dose dabigatran etexilate in healthy adults

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Abstract

Objective Darunavir (DRV) is a P-glycoprotein (P-gp) inhibitor. Dabigatran etexilate, prodrug of the anticoagulant dabigatran, is a P-gp probe substrate. This study evaluated the effect of single and multiple doses of DRV, coadministered with cobicistat (COBI) or ritonavir (rtv), on the pharmacokinetics (PK) of single-dose dabigatran etexilate.

Methods This was an open-label, fixed-sequence, single-center, 2-panel, phase 1 study in which healthy adult participants were equally divided over 2 panels. In panel 1, participants received single and multiple doses of DRV/COBI 800/150 mg coadministered with single-dose dabigatran etexilate 150 mg. In panel 2, participants received single and multiple doses of DRV 800 mg + rtv 100 mg coadministered with single-dose dabigatran etexilate 150 mg. Key PK parameters evaluated were maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) for free and total dabigatran.

Results Overall, 28 participants were enrolled and treated ($n = 14$ per panel). Dabigatran C_{max} and AUC_{inf} increased 2.64-fold after a single dose of DRV/COBI and 1.99- and 1.88-fold, respectively, after multiple doses of DRV/COBI. Dabigatran C_{max} and AUC_{inf} increased 1.64- and 1.72-fold, respectively, after a single dose of DRV + rtv and 1.22- and 1.18-fold, respectively, after multiple doses of DRV + rtv. In both panels, the most commonly reported adverse events were diarrhea and headache.

Conclusion Findings of increased dabigatran exposure with DRV/COBI or DRV + rtv coadministration indicate an inhibitory effect of single-dose boosted DRV on P-gp, and a mixed inhibitory/inductive effect of multiple doses of boosted DRV on P-gp.

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Keywords Darunavir, Ritonavir, Cobicistat, Dabigatran, Drug-drug interaction

Introduction

Protease inhibitor (PI)–based regimens have become cornerstones in the treatment of human immunodeficiency virus (HIV)–1, demonstrating virologic potency, durability in treatment-naïve patients, and a high genetic barrier to resistance development (Panel on Antiretroviral Guidelines for Adults and Adolescents and Department of Health and Human Services 2022). Darunavir (DRV),

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which is primarily metabolized by cytochrome P450 3A (CYP3A), is a PI indicated for the treatment of HIV-1 in adult and pediatric patients aged ≥ 3 years that must be coadministered with pharmacokinetic (PK) enhancers, such as cobicistat (COBI) or ritonavir (rtv) in combination with other antiretroviral (ARV) agents (PREZISTA® 2019). Rtv is a strong CYP3A inhibitor originally developed as a standalone PI at high doses, though it is now widely used at lower doses as a PK enhancer to increase systemic concentrations of other ARVs (Hill and Balkin 2009; Panel on Antiretroviral Guidelines for Adults and Adolescents and Department of Health and Human Services 2022). COBI is a selective, potent inhibitor of CYP3A without antiviral activity, but with a chemical profile that allows for coformulation with other agents (Xu et al. 2010). A fixed-dose combination of DRV/COBI 800/150 mg is approved for the once-daily treatment of HIV-1 in treatment-naïve and treatment-experienced adults with no DRV resistance-associated mutations (PREZCOBIX® 2018).

DRV in combination with rtv or COBI inhibits CYP3A, CYP2D6 and the efflux transporter P-glycoprotein (P-gp) (PREZISTA® 2019; TYBOST 2023). Coadministration of DRV/COBI or DRV + rtv with drugs that are primarily metabolized by CYP3A or CYP2D6 or are transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and the occurrence of adverse events (AEs). Dabigatran etexilate is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism and for the treatment, risk reduction, and prophylaxis of deep vein thrombosis and pulmonary embolism. Dabigatran etexilate, the prodrug of dabigatran, is a probe substrate of P-gp. After oral administration, dabigatran etexilate is converted to dabigatran via esterase-catalyzed hydrolysis. Dabigatran is subject to conjugation and circulates in plasma in its unconjugated (free) form and in equipotent dabigatran glucuronide conjugates. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Therefore, dabigatran etexilate is a suitable substrate to selectively assess the drug-drug interaction with DRV/COBI or DRV + rtv at the level of intestinal P-gp transport (PRADAXA 2023).

The primary objective of this analysis was to evaluate the effect of single and multiple doses of DRV in combination with COBI or rtv on the PK of single-dose dabigatran etexilate when coadministered in healthy adult participants.

Methods

Study design and treatments

This was an open-label, fixed-sequence, single-center, 2-panel, phase 1 study conducted in healthy adult participants between January 3, 2020, and April 1, 2021 (Fig. 1). Each panel consisted of a screening period of approximately 4 weeks, an open-label treatment period of approximately 3 weeks, and an end-of-study/follow-up period of 7 to 10 days after the last drug intake. The study duration was approximately 8 weeks. In panel 1, participants received the following treatments: a single dose of dabigatran etexilate 150 mg on Day 1 (treatment A), a single dose of DRV/COBI 800/150 mg and a single dose of dabigatran etexilate 150 mg on Day 4 (treatment B), and once-daily DRV/COBI 800/150 mg from Days 5 to 20 and a single dose of dabigatran etexilate 150 mg on Day 18 (treatment C). In panel 2, participants received the following treatments: a single dose of dabigatran etexilate 150 mg on Day 1 (treatment D); single doses of DRV 800 mg, rtv 100 mg, and dabigatran etexilate 150 mg on Day 4 (treatment E); and once-daily DRV 800 mg + rtv 100 mg from Days 5 to 20 and a single dose of dabigatran etexilate 150 mg on Day 18 (treatment F). Panels 1 and 2 were conducted in parallel; participants were not randomized but rather recruited separately for

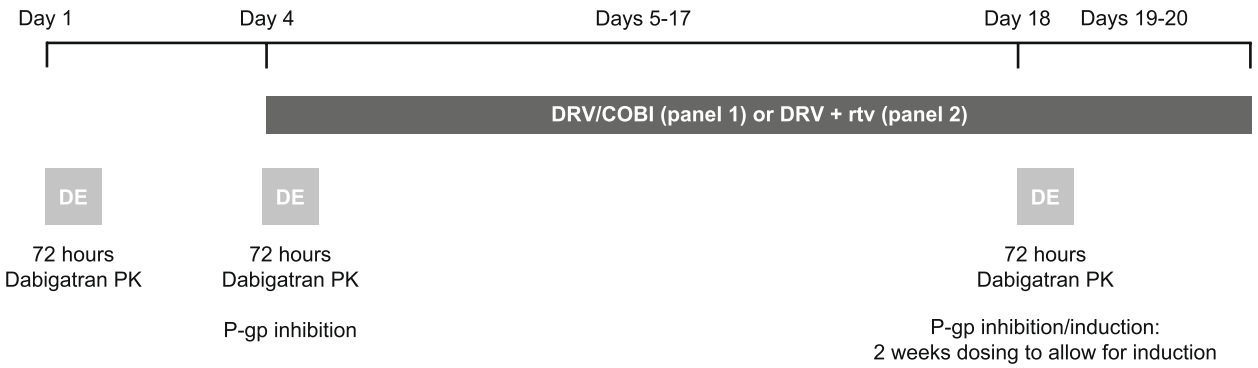

Fig. 1 Study design. DE, dabigatran etexilate; DRV/COBI, darunavir/cobicistat; DRV + rtv, darunavir + ritonavir; PK, pharmacokinetics; P-gp, P-glycoprotein

each panel. Participants enrolled in 1 panel of the study were not allowed to participate in the other panel. During the open-label treatment phase, all drug intakes took place under fed conditions.

The study was conducted in accordance with Good Clinical Practice following the principles of the Declaration of Helsinki, with protocol approvals from an Independent Ethics Committee and written informed consent obtained from participants.

Participants

Participants were eligible to enroll in the study if they were aged 18 to 60 years (inclusive), had a body mass index (BMI) between 18.0 and 30.0 kg/m^2 (inclusive) and bodyweight not < 50.0 kg, and were healthy on the basis of physical examination, medical history, vital signs, clinical laboratory tests, and electrocardiogram (ECG) performed at screening. Participants were excluded from the study if they had a clinically significant medical illness (or any history of such illness), any history of clinically significant skin disease (such as dermatitis, eczema, drug rash, psoriasis, food allergy, or urticaria), or any clinically significant abnormalities during physical examination, vital signs, or 12-lead ECG at screening.

Assessments and procedures

The primary objective of the current analysis was to evaluate the effect of single and repeated doses of DRV in combination with COBI or rtv on the PK of single-dose dabigatran etexilate, measured in plasma as free and total dabigatran, when coadministered in healthy participants. The magnitude of P-gp inhibition and/or induction by DRV/COBI or DRV + rtv was evaluated by assessing the exposure of the probe substrate dabigatran etexilate. Coadministration of a single dose of dabigatran etexilate with a single dose of DRV/COBI or DRV + rtv assessed the inhibitory effect on P-gp, while coadministration of repeated doses of DRV/COBI or DRV + rtv assessed the mixed inhibitory/inductive effect on P-gp.

Key PK parameters evaluated in this study included maximum plasma concentration (C_{max}) of dabigatran and area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) for free and total dabigatran. For safety assessments, incidences of AEs were presented by treatment and overall. Other safety parameters included laboratory abnormalities and change from baseline in vital signs and ECG measurements. Safety and tolerability were evaluated throughout the study.

Blood samples for determination of DRV/COBI or DRV + rtv and dabigatran (free and total) plasma concentrations were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 18, 24, 36, 48, and 72 h post-dose. Blood samples were analyzed using validated, specific, and sensitive high-performance liquid chromatography–tandem mass spectroscopy methods.

Statistical analysis

Intraindividual coefficients of variation (CVs) for PK parameters (C_{max}, area under the plasma concentration-time curve from time zero to the last measurable concentration [AUC_{last}], and AUC_{inf}) of dabigatran were estimated to be < 26% in healthy participants under fed conditions based on the literature. Using an intraindividual CV of 26% for C_{max}, AUC_{last}, and AUC_{inf} of free and total dabigatran, a sample size of 12 completed participants per panel was deemed to be sufficient for the point estimate of the ratio of dabigatran (free and total) PK parameter geometric means of test versus reference treatments (dabigatran etexilate with and without DRV/COBI [panel 1], dabigatran etexilate with and without DRV + rtv [panel 2], respectively) to fall within 82.8% and 120.8% of the true value with 90% confidence. To account for premature discontinuations (assuming approximately 10% dropout rate), 28 participants (14 per panel) were recruited. PK was analyzed using Phoenix™ WinNonlin® (Certara L.P., Princeton, NJ, US, version 8.3). Noncompartmental analysis was applied for the PK analysis, and SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) was utilized. Descriptive statistics were calculated for the plasma concentrations of DRV and COBI (panel 1) or DRV and rtv (panel 2) and dabigatran (free and total) at each time point, as well as for the derived PK parameters. All participants who received ≥ 1 dose of study drug and had ≥ 1 plasma concentration measurement were included in the PK analysis.

The primary PK parameters for statistical analysis were the log-transformed C_{max} and AUC_{inf} for free and total dabigatran. All observations for test and reference were included in the statistical analysis. The AUC_{inf} would be rejected as primary parameter if > 50% of participants did not have an estimable AUC_{inf}. For each panel, a mixed effects model was fit to the log-transformed primary PK parameters (C_{max} and AUC_{inf}) with treatment as a fixed effect and participant as a random effect. The least square means and intraindividual standard deviations (SDs) were used to estimate the difference in means on the log scale and the associated 90% confidence intervals (CIs) for the following comparisons in each panel for free and total dabigatran: for panel 1, treatment B (dabigatran etexilate and single-dose DRV/COBI) versus treatment A (dabigatran etexilate alone) and treatment C (dabigatran etexilate and multiple doses of DRV/COBI) versus treatment A (dabigatran etexilate alone), and for panel 2, treatment E (dabigatran etexilate and single-dose DRV + rtv) versus

treatment D (dabigatran etexilate alone) and treatment F (dabigatran etexilate and multiple doses of DRV + rtv) versus treatment D (dabigatran etexilate alone).

All participants who were enrolled and received ≥ 1 dose of study drug were included in the safety and tolerability analysis. Baseline for all laboratory evaluations, vital signs, and ECG measurements was defined as the last evaluation done before the first study drug administration. Treatment-emergent AEs were defined as AEs with onset during the treatment phase or those that were a consequence of a preexisting condition that worsened since baseline. Treatment-emergent AEs were coded in accordance with the *Medical Dictionary for Regulatory Activities* (MedDRA) version 23.1.

Results

Study population

A total of 28 healthy adult participants were enrolled and treated in the study ($n = 14$ for each panel); 1 participant in panel 2 did not complete the study due to an AE (grade 2 rash). Demographics and baseline characteristics were comparable across panels (Table 1). All participants were White, except for 1 (7.1%) participant in panel 2 characterized as "multiple."

There were no participants of Hispanic or Latino ethnicity.

Table 1 Demographics and baseline characteristics

	Panel 1[a] ($n = 14$)	Panel 2[b] ($n = 14$)
Age, mean (SD), years	46.6 (11.5)	46.4 (14.3)
Female, n (%)	5 (35.7)	9 (64.3)
Race, n (%)		
White	14 (100)	13 (92.9)
Multiple	0	1 (7.1)
Ethnicity, n (%)		
Not Hispanic or Latino	14 (100)	14 (100)
Weight, mean (SD), kg	76.1 (11.3)	73.0 (12.6)
Height, mean (SD), cm	175 (8.2)	169 (9.3)
BMI, mean (SD), kg/m^2	24.7 (2.4)	25.5 (2.7)

BMI body mass index, *COBI* cobicistat, *DRV* darunavir, *rtv* ritonavir, *SD* standard deviation

[a] Panel 1: treatment A, dabigatran etexilate 150 mg on Day 1; treatment B, DRV/COBI 800/150 mg and dabigatran etexilate 150 mg on Day 4; treatment C, DRV/COBI 800/150 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

[b] Panel 2: treatment D, dabigatran etexilate 150 mg on Day 1; treatment E, DRV + rtv 800/100 mg and dabigatran etexilate 150 mg on Day 4; treatment F, DRV + rtv 800/100 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

PK of dabigatran when coadministered with DRV/COBI (Panel 1)

Mean plasma concentrations of total dabigatran over time, administered alone and coadministered with single and multiple doses of DRV/COBI, are presented in Fig. 2a. On average, quantifiable levels of total dabigatran were obtained between 1 and 48 h after dosing for treatments A and C and between 1 and 72 h after dosing for treatment B. For all treatments, maximum concentrations were reached 4 h post-dose. Concentrations increased when dabigatran etexilate was coadministered with DRV/COBI, with the highest increase observed after a single dose of DRV/COBI and lesser increases observed after multiple doses of DRV/COBI. Individual total dabigatran PK parameters and statistical analysis on primary PK parameters are presented in Table 2. Total dabigatran C_{max} and AUC_{inf} increased 2.64-fold after a single dose of DRV/COBI, and 1.99- and 1.88-fold, respectively, after multiple doses of DRV/COBI compared with dabigatran alone. Mean half-life ($t_{1/2}$) of dabigatran was comparable with or without DRV/COBI. PK results were similar for free dabigatran exposure when coadministered with DRV/COBI (Supplementary Table 1).

PK of dabigatran when coadministered with DRV + rtv (Panel 2)

Mean plasma concentrations of total dabigatran over time, administered alone and coadministered with single and multiple doses of DRV + rtv, are presented in Fig. 2b. On average, quantifiable levels of total dabigatran were obtained between 1 and 48 h after dosing for all treatments. Maximum concentrations were reached 3 (treatment D), 4 (treatment F), or 5 (treatment E) hours after dosing. As was observed when dabigatran etexilate was coadministered with DRV/COBI, concentrations increased when dabigatran etexilate was coadministered with DRV + rtv, with the highest increase observed after a single dose of DRV + rtv and lesser increases observed after multiple doses of DRV + rtv. As seen in Table 2, total dabigatran C_{max} and AUC_{inf} increased 1.64- and 1.72-fold, respectively, after a single dose of DRV + rtv, and 1.22- and 1.18-fold, respectively, after multiple doses of DRV + rtv compared with dabigatran alone. Mean $t_{1/2}$ of dabigatran was comparable with or without DRV + rtv. PK results were similar for free dabigatran exposure when coadministered with DRV + rtv (Supplementary Table 1).

Safety

A summary of all AEs is provided in Table 3. No serious AEs, grade 3 or 4 AEs, or fatalities were reported.

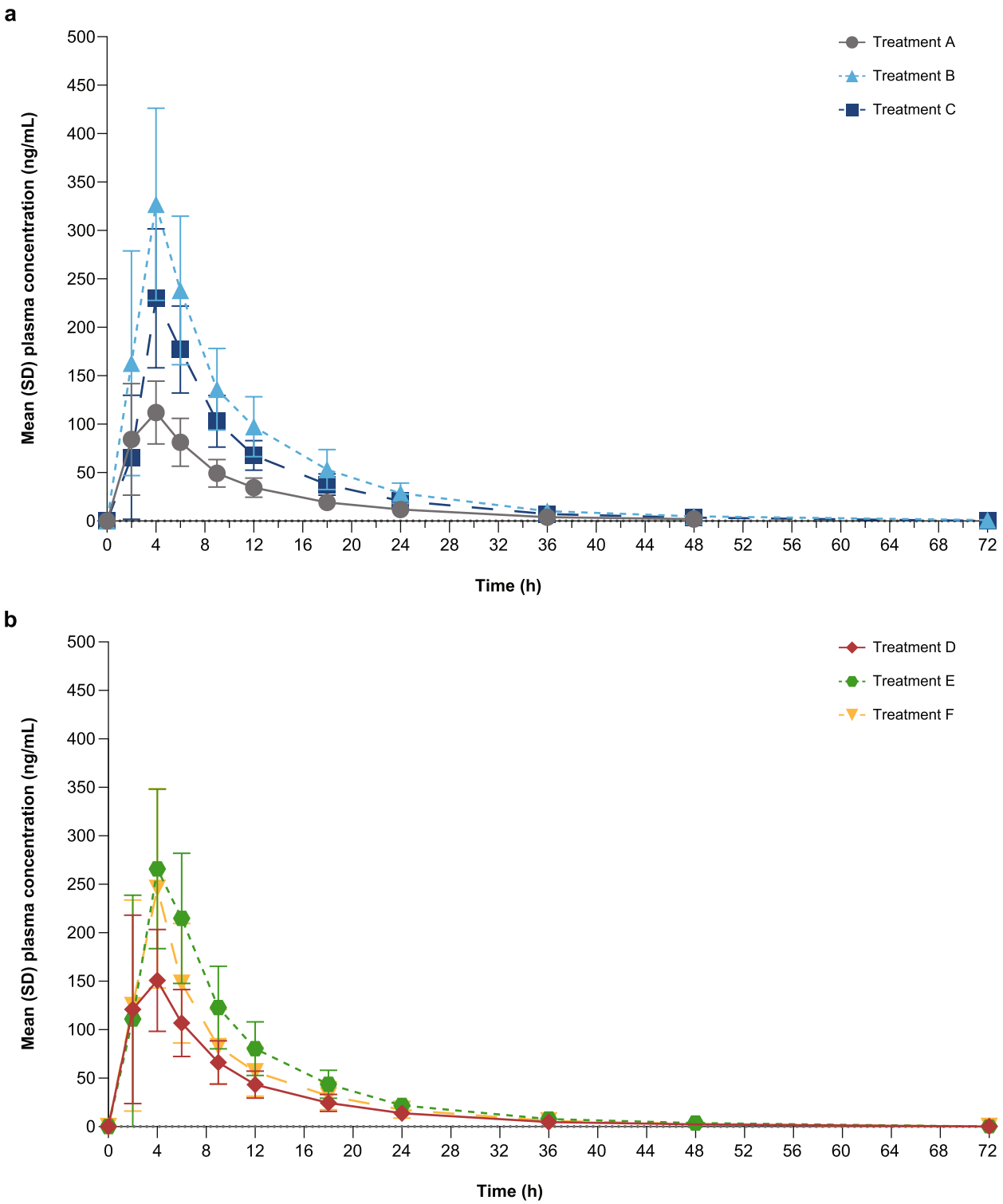

Fig. 2 Mean total dabigatran plasma concentrations versus time for (a) panel 1[a] and (b) panel 2[b]. COBI, cobicistat; DRV, darunavir; rtv, ritonavir; SD, standard deviation. [a]Panel 1: treatment A, dabigatran etexilate 150 mg on Day 1; treatment B, DRV/COBI 800/150 mg and dabigatran etexilate 150 mg on Day 4; treatment C, DRV/COBI 800/150 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18. [b]Panel 2: treatment D, dabigatran etexilate 150 mg on Day 1; treatment E, DRV + rtv 800/100 mg and dabigatran etexilate 150 mg on Day 4; treatment F, DRV + rtv 800/100 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

Table 2 PK parameters and statistical analysis summary of dabigatran (total) exposure for Panels 1 and 2

Panel 1[a]				
Parameter		**Treatment A (*n* = 14)**	**Treatment B (*n* = 14)**	**Treatment C (*n* = 14)**
C_{max}, mean (SD), ng/mL		130 (41.6)	344 (96.8)	254 (62.5)
t_{max}, median (range), h		3.00 (1.50-5.00)	4.00 (3.00-5.00)	4.00 (3.00-5.02)
AUC_{inf}, mean (SD), ng·h/mL		1207 (325)	3233 (1054)	2252 (520)
$t_{1/2}$, mean (SD), h		9.3 (1.8)	10.7 (2.7)	10.7 (3.0)
Parameter	**Comparison**	**Geometric LSM ratio (%)**	**90% CI (%)**	**Intra-individual CV%**
C_{max}, ng/mL	Treatment B vs A	264.25	(228.67-305.36)	22.7
	Treatment C vs A	198.64	(171.90-229.55)	
AUC_{inf}, ng·h/mL	Treatment B vs A	263.84	(232.39-299.55)	19.9
	Treatment C vs A	187.80	(165.41-213.21)	
Panel 2[b]				
Parameter		**Treatment D (*n* = 14)**	**Treatment E (*n* = 14)**	**Treatment F (*n* = 13)**
C_{max}, mean (SD), ng/mL		186 (65.4)	301 (95.2)	266 (116)
t_{max}, median (range), h		3.00 (1.00-5.00)	4.01 (2.02-5.02)	4.02 (1.52-5.00)
AUC_{inf}, mean (SD), ng·h/mL		1565 (509)	2667 (847)	2068 (877)
$t_{1/2}$, mean (SD), h		8.8 (1.1)	9.8 (2.1)	8.9 (1.8)
Parameter	**Comparison**	**Geometric LSM ratio (%)**	**90% CI (%)**	**Intra-individual CV%**
C_{max}, ng/mL	Treatment E vs D	164.22	(120.82-223.20)	50.3
	Treatment F vs D	121.84	(88.99-166.83)	
AUC_{inf}, ng·h/mL	Treatment E vs D	172.20	(132.73-223.41)	42.0
	Treatment F vs D	117.50	(90.00-153.41)	

AUC_{inf} area under the curve from time zero to infinity, *CI* confidence interval, *C_{max}* maximum plasma concentration, *COBI* cobicistat, *DRV* darunavir, *LSM* least squares mean, *rtv* ritonavir, *SD* standard deviation, *$t_{1/2}$* half-life, *t_{max}* time at C_{max}

[a] Panel 1: treatment A, dabigatran etexilate 150 mg on Day 1; treatment B, DRV/COBI 800/150 mg and dabigatran etexilate 150 mg on Day 4; treatment C, DRV/COBI 800/150 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

[b] Panel 2: treatment D, dabigatran etexilate 150 mg on Day 1; treatment E, DRV + rtv 800/100 mg and dabigatran etexilate 150 mg on Day 4; treatment F, DRV + rtv 800/100 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

Overall, there was 1 AE that led to study discontinuation (grade 2 rash reported during treatment F in panel 2).

In panel 1, 3 (21.4%), 8 (57.1%), and 6 (42.9%) participants reported ≥ 1 treatment-emergent AE during treatments A, B, and C, respectively. The majority of treatment-emergent AEs was classified as gastrointestinal disorders and nervous system disorders, occurring during treatment A (1 [7.1%] participant who experienced a nervous system disorder), treatment B (3 [21.4%] and 2 [14.3%] participants, respectively), and treatment C (2 [14.3%] and 2 [14.3%] participants, respectively). All reported treatment-emergent AEs were grade 1 in severity.

In panel 2, 3 (21.4%), 13 (92.9%), and 6 (46.2%) participants reported ≥ 1 treatment-emergent AE during treatments D, E, and F, respectively. The majority of treatment-emergent AEs was classified as gastrointestinal disorders, nervous system disorders, and skin and subcutaneous tissue disorders, occurring during treatment D (1 [7.1%] participant who experienced a nervous system disorder and 1 [7.1%] participant who experienced a skin and subcutaneous tissue disorder), treatment E (10 [71.4%], 6 [42.9%], and 3 [21.4%] participants, respectively), and treatment F (3 [23.1%] participants who experienced a gastrointestinal disorder and 3 [23.1%] participants who experienced a nervous system disorder). All reported treatment-emergent AEs were grade 1, except for grade 2 rash reported in 1 (7.1%) participant during treatment E.

All treatment-emergent graded laboratory abnormalities were grade 1 or 2 in severity, except for a grade 4 high potassium reported by 1 (7.1%) participant in panel 1 during treatment B and a grade 3 high lipase reported by 1 (7.7%) participant in panel 2 during treatment F. These laboratory abnormalities were not confirmed on repeat assessment, and no treatment-related pattern was detected.

In both panels, no trends over time or median changes from baseline for vital sign parameters were observed. Median changes over time in ECG

Table 3 Summary of adverse events for Panels 1 and 2

AEs, n (%)	Panel 1[a]			Panel 2[b]		
	Treatment A (*n* = 14)	Treatment B (*n* = 14)	Treatment C (*n* = 14)	Treatment D (*n* = 14)	Treatment E (*n* = 14)	Treatment F (*n* = 13)
AEs	3 (21.4)	8 (57.1)	6 (42.9)	3 (21.4)	13 (92.9)	6 (46.2)
AEs occurring in > 10% of participants in any group						
Diarrhea	0	2 (14.3)	1 (7.1)	0	7 (50.0)	2 (15.4)
Headache	1 (7.1)	1 (7.1)	2 (14.3)	1 (7.1)	4 (28.6)	3 (23.1)
Abdominal discomfort	0	0	1 (7.1)	0	5 (35.7)	0
Dyspepsia	0	2 (14.3)	1 (7.1)	0	0	1 (7.7)
Head discomfort	0	1 (7.1)	2 (14.3)	0	0	0
Nausea	0	0	1 (7.1)	0	2 (14.3)	0
Myalgia	0	0	1 (7.1)	1 (7.1)	2 (14.3)	0
Pruritus	0	0	0	0	2 (14.3)	0
Hematoma	0	2 (14.3)	0	0	0	0
AEs grade ≥ 3	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0

AE adverse event, *COBI* cobicistat, *DRV* darunavir, *rtv* ritonavir

[a] Panel 1: treatment A, dabigatran etexilate 150 mg on Day 1; treatment B, DRV/COBI 800/150 mg and dabigatran etexilate 150 mg on Day 4; treatment C, DRV/COBI 800/150 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

[b] Panel 2: treatment D, dabigatran etexilate 150 mg on Day 1; treatment E, DRV + rtv 800/100 mg and dabigatran etexilate 150 mg on Day 4; treatment F, DRV + rtv 800/100 mg (once daily) on Days 5 to 20 and dabigatran etexilate 150 mg on Day 18

parameters were generally minor and were not considered to be clinically meaningful.

Discussion

This phase 1 study assessed the effect of single and multiple doses of DRV in combination with COBI or rtv on the PK of single-dose dabigatran etexilate in healthy adult participants in order to evaluate the drug-drug interaction potential at the level of P-gp transport. P-gp is highly expressed on the apical surface of many tissues, but its greatest effect on drug-drug interactions appears to be via inhibition of intestinal P-gp (Kumar et al. 2017; Chu et al. 2018).

DRV in combination with rtv or COBI inhibits CYP3A, CYP2D6 and P-gp (PRADAXA 2023). Dabigatran etexilate is a probe substrate of P-gp and widely used in drug-drug interaction studies (Kumar et al. 2017; Chu et al. 2018; US Food and Drug Administration 2022). The drug is rapidly absorbed and transformed by intestinal carboxylesterase (CES) 2 and hepatic CES1 to dabigatran, which is not transported by P-gp. Dabigatran is subject to glucuronidation in the liver, forming active acyl glucuronides, and is primarily eliminated as unchanged drug via passive glomerular filtration (Chu et al. 2018). Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes (PRADAXA 2023). Therefore, the drug-drug interaction assessed in this study can be considered to represent the specific effect of DRV/COBI or DRV + rtv on intestinal P-gp transport, as CYP450 enzymes are not involved in the metabolic pathway of dabigatran.

In both study panels, the increase in total dabigatran exposure after a single dose of DRV/COBI or DRV + rtv demonstrates the inhibitory effect of DRV/COBI or DRV + rtv on P-gp. As expected, the mean $t_{1/2}$ of dabigatran did not change when co-administered with DRV/COBI or DRV + rtv, confirming that the drug-drug interaction was limited to the absorption of dabigatran etexilate (i.e., inhibition of intestinal P-gp).

Multiple doses of DRV/COBI or DRV + rtv also led to an increase in dabigatran exposure; however, this increase was lower than after single doses of DRV/COBI or DRV + rtv, indicating mixed inhibitory/inductive effects on P-gp. While rtv inhibition of P-gp may decrease over time (NORVIR 2023) and there is evidence that rtv induces P-gp (Chan et al. 2013), COBI is not expected to induce P-gp (TYBOST 2023). Thus, DRV likely drove the net decrease in P-gp inhibition observed with multiple once-daily DRV/COBI doses versus a single DRV/COBI dose. Indeed, DRV induction of both P-gp expression and activity has been reported based on in vitro human cell culture experiments using brain microvessel endothelial cells (Chan et al. 2013), blood cells (Tempestilli et al. 2013), and colon adenocarcinoma cells (Konig et al. 2010).

Divergent effects of COBI versus rtv on dabigatran exposure were also observed in a previous study assessing the influence of these agents individually on the P-gp

transport of dabigatran etexilate (Kumar et al. 2017). In the earlier study, after multiple once-daily doses of COBI or rtv, simultaneous administration of COBI with dabigatran etexilate resulted in a 2.27-fold increase in both dabigatran C_{max} and AUC_{inf} compared with dabigatran etexilate administered alone; there was no significant impact on dabigatran PK with the simultaneous administration of rtv and dabigatran etexilate (1.13- and 1.15-fold increased dabigatran C_{max} and AUC_{inf}, respectively). Comparing these results to the changes in dabigatran PK observed in the current study after multiple doses of COBI or rtv in the presence of DRV further illustrates the effect of DRV on P-gp transport. The addition of DRV attenuated the net dabigatran exposure increase reported after multiple doses of COBI alone, while it enhanced the dabigatran exposure increase observed with rtv. Such results additionally suggest a combined inhibitory/inductive effect of DRV on P-gp.

The impact of boosted DRV on dabigatran exposure observed in the current study is within the range of that observed with other P-gp inhibitors. For example, ketoconazole has been shown to increase total dabigatran C_{max} and AUC_{inf} values by 2.35- and 2.38-fold, respectively, after a single ketoconazole oral dose, and by 2.49- and 2.53-fold, respectively, after multiple once-daily ketoconazole oral doses (Boehringer Ingelheim 2009); the effects of ketoconazole on the PK of free and total dabigatran were similar (Boehringer Ingelheim 2009). The impact of verapamil on dabigatran exposure differs with single versus multiple dosing (Hartter et al. 2013; PRADAXA 2023). Verapamil has been shown to increase total dabigatran C_{max} and AUC_{inf} values by 2.79- and 2.43-fold, respectively, when dabigatran etexilate is administered 1 h after a single dose of verapamil, while dabigatran exposure increased 1.63- and 1.54-fold, respectively, when dabigatran etexilate is administered 1 h before verapamil given as multiple twice-daily doses (Hartter et al. 2013). The attenuated effect of multiple doses of verapamil on dabigatran exposure was suggested to be attributed to induction of P-gp expression after multiple dosing.

Coadministration of DRV/COBI or DRV + rtv and dabigatran was generally safe and well tolerated in healthy adult participants. In both panels, the most frequently reported treatment-emergent AEs were diarrhea and headache. No serious AEs, grade 3 or 4 AEs, or fatalities were reported.

In conclusion, the results of this study demonstrate increased dabigatran exposure with DRV/COBI or DRV + rtv coadministration as a result of an inhibitory effect of single-dose boosted DRV on P-gp and a mixed inhibitory/inductive effect of multiple doses of boosted DRV on P-gp.

Abbreviations

AE	Adverse event
ARV	Antiretroviral
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last measurable concentration
BMI	Body mass index
CES	Carboxylesterase
CI	Confidence interval
C_{max}	Maximum plasma concentration
COBI	Cobicistat
CV	Coefficient of variation
CYP3A	Cytochrome P450 3A
DRV	Darunavir
ECG	Electrocardiogram
HIV	Human immunodeficiency virus
MedDRA	*Medical Dictionary for Regulatory Activities*
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
rtv	Ritonavir
SD	Standard deviation
$t_{1/2}$	Half-life

Supplementary Information

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Supplementary Material 1.

Authors' contributions

SVH was the Clinical Pharmacology Leader for this study, responsible for pharmacokinetic-related study design and for the analysis and interpretation of the pharmacokinetic data. EVL was the Study Responsible Physician for this study. JA served as the lead statistician, responsible for analyzing and interpreting the findings of the inferential statistical analysis. MP was the Global Trial Leader, responsible for the operational aspects of this study. MJCK was the Principal Investigator for this study. CP was the study manager of the trial, responsible for coordination at the study site. All authors read, provided critical review of, and approved the final manuscript.

Declarations

Availability of data and materials

Although these data are not currently publicly available for sharing, requests for sharing can be sent to the corresponding author and will be evaluated on an individual basis.

Competing interests

SVH, EVL, JA, MP, MJCK, and CP are employees of Janssen and may be stockholders of Johnson & Johnson.

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Authors' information

Not applicable.

Ethics approval and consent to participate
This study was conducted in accordance with Good Clinical Practice following the principles of the Declaration of Helsinki, with protocol approval by Comité voor medische ethiek UZA and written informed consent obtained from participants.

Consent for publication
Not applicable.

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