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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

Sandy Van Hemelryck,[1,*] Erika Van Landuyt,[1] Jay Ariyawansa,[1] Martyn Palmer,[1] Martine J.C. Kothe,[2] Caroline Pollefliet[2]

[1]Janssen Pharmaceutica NV, Beerse, Belgium; [2]Clinical Pharmacology Unit, Janssen Research & Development, Merksem, Belgium

*Presenting author.

Introduction

- DRV is a PI indicated for the treatment of HIV-1 in adult and paediatric patients aged ≥3 years that must be coadministered with a PK enhancer (such as COBI or rtv) in combination with other ARV agents[1-4]
- An FDC 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[5]
- DRV, rtv, and COBI are inhibitors of the efflux transporter P-gp; coadministration of DRV/COBI or DRV + rtv with drugs that are primarily transported by P-gp may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and AEs[1,6]
- Dabigatran etexilate, the prodrug of the direct thrombin inhibitor dabigatran, is a probe substrate of P-gp and circulates in plasma in the unconjugated (free) form of dabigatran and as equipotent dabigatran glucuronide conjugates[7]

Objective

- 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

- TMC114FD1HTX1002 (ClinicalTrials.gov Identifier: NCT04208061) was an open-label, fixed-sequence, single-centre, 2-panel, phase 1 study conducted in healthy adult participants aged 18 to 60 years (inclusive) between 3 January 2020 and 1 April 2021
  - 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 and once-daily rtv 100 mg from Days 5 to 20 and a single dose of dabigatran etexilate 150 mg on Day 18 (treatment F)
- During the open-label treatment phase, all drug intakes took place under fed conditions

Assessments

- Key PK parameters evaluated included C_{max} of dabigatran and AUC_{inf} for free and total dabigatran
- Safety was evaluated as incidences of AEs, presented by treatment and overall

Statistical Analysis

- Using an intraindividual CV of 26% for AUC_{inf} and C_{max} 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] and 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
- Descriptive statistics were calculated for the plasma concentrations of DRV/COBI (panel 1) or DRV + rtv (panel 2) and dabigatran (free and total) at each time point, as well as for the derived PK parameters
- The LSM and intraindividual SD were used to estimate the difference in means on the logarithmic scale and the associated 90% CI for the following comparisons in each panel for free and total dabigatran:
  - Panel 1: treatment B (single-dose DRV/COBI + dabigatran etexilate) versus treatment A (dabigatran etexilate alone) and treatment C (multiple doses of DRV/COBI + dabigatran etexilate) versus treatment A (dabigatran etexilate alone)
  - Panel 2: treatment E (single-dose DRV + rtv + dabigatran etexilate) versus treatment D (dabigatran etexilate alone) and treatment F (multiple doses of DRV + rtv + dabigatran etexilate) 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

Results

Study Population

- A total of 28 healthy adult participants were enrolled and treated in the study (n = 14 for each panel)
- Demographic and baseline characteristics were comparable across panels (**Table 1**)

Table 1. Demographic and baseline characteristics

	Panel 1* (n = 14)	Panel 2† (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)

*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.
†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)

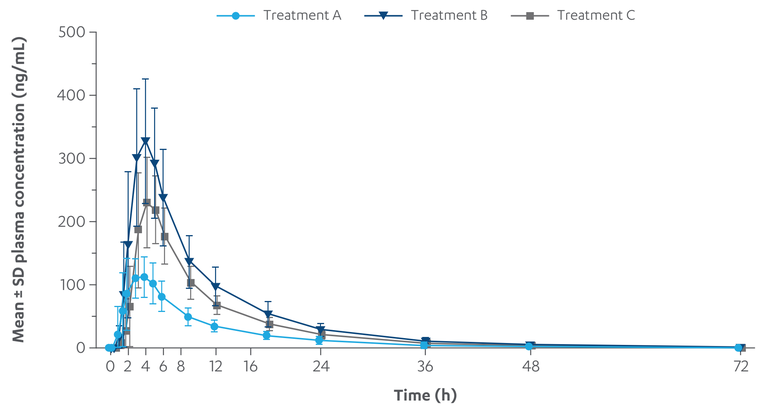
- Total dabigatran C_{max} and AUC_{inf} increased 2.64-fold after a single dose of DRV/COBI administered alone and 1.99- and 1.88-fold, respectively, after multiple doses of DRV/COBI compared with dabigatran etexilate alone (**Table 2**)
- Mean plasma concentrations of total dabigatran over time, administered alone and coadministered with single and multiple doses of DRV/COBI, are presented in **Figure 1**
- Results were similar for free dabigatran exposure when coadministered with DRV/COBI

Table 2. PK parameters and statistical analysis summary of dabigatran (total) after administration of dabigatran etexilate alone (Day 1) and in combination with single (Day 4) and multiple (Day 18) doses of DRV/COBI (panel 1)*

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		1,207 (325)	3,233 (1,054)	2,252 (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 (%)**	**Intraindividual CV%**
C_{max}, ng/mL				22.7
	Treatment B vs A	264.25	228.67-305.36	
	Treatment C vs A	198.64	171.90-229.55	
AUC_{inf}, ng·h/mL				19.9
	Treatment B vs A	263.84	232.39-299.55	
	Treatment C vs A	187.80	165.41-213.21	

*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.

Figure 1. Mean plasma concentrations of total dabigatran versus time (panel 1)*



*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.

PK of Dabigatran When Coadministered With DRV + rtv (Panel 2)

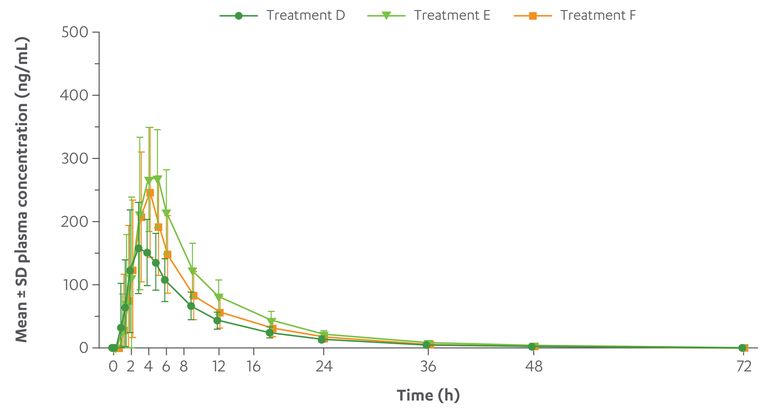
- Total dabigatran C_{max} and AUC_{inf} increased 1.64- and 1.72-fold, respectively, after a single dose of DRV + rtv and 1.22- and 1.18-fold, respectively, after multiple doses of DRV + rtv compared with dabigatran etexilate administered alone (**Table 3**)
- Mean plasma concentrations of total dabigatran over time, administered alone and coadministered with single and multiple doses of DRV + rtv, are presented in **Figure 2**
- Results were similar for free dabigatran exposure when coadministered with DRV + rtv

Table 3. PK parameters and statistical analysis summary of dabigatran (total) after administration of dabigatran etexilate alone (Day 1) and in combination with single (Day 4) and multiple (Day 18) doses of DRV + rtv (panel 2)*

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		1,565 (509)	2,667 (847)	2,068 (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 (%)**	**Intraindividual CV%**
C_{max}, ng/mL				50.3
	Treatment E vs D	164.22	120.82-223.20	
	Treatment F vs D	121.84	88.99-166.83	
AUC_{inf}, ng·h/mL				42.0
	Treatment E vs D	172.20	132.73-223.41	
	Treatment F vs D	117.50	90.00-153.41	

*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.

Figure 2. Mean plasma concentrations of total dabigatran versus time (panel 2)*



*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.

Safety

- In panel 1, 3 (21.4%), 8 (57.1%), and 6 (42.9%) participants reported ≥1 TEAE during treatments A, B, and C, respectively (all grade 1; **Table 4**)
- In panel 2, 3 (21.4%), 13 (92.9%), and 6 (46.2%) participants reported ≥1 TEAE during treatments D, E, and F, respectively (all grade 1 except for 1 [7.1%] grade 2 rash reported during treatment E)
- One (7.1%) participant in panel 2 prematurely terminated study participation during treatment F due to an AE of grade 2 rash considered related to DRV + rtv
- There were 4 treatment-related AEs reported in panel 1 (dabigatran-related AE, n = 2; DRV/COBI-related AE, n = 2) and 11 reported in panel 2 (dabigatran-related AE, n = 1; DRV-related AE, n = 5; rtv-related AE, n = 5)
- No grade 3/4 TEAEs, serious AEs, or fatalities were reported

Table 4. Summary of AEs for panels 1 and 2

AEs, n (%)	Panel 1*			Panel 2†		
	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						
Diarrhoea	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
Haematoma	0	2 (14.3)	0	0	0	0
Grade ≥3 AEs	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0

*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.
†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.

Key Findings

- Total dabigatran exposure increased after a single dose of DRV/COBI or DRV + rtv, confirming the inhibitory effects of DRV/COBI and DRV + rtv on P-gp
- Multiple doses of DRV/COBI or DRV + rtv led to an increase in dabigatran exposure; however, this increase was lower than after single doses of DRV/COBI or DRV + rtv, indicating a mixed inhibitory/inductive effect on P-gp
- Coadministration of DRV/COBI or DRV + rtv and dabigatran etexilate was generally safe and well tolerated in healthy adult participants

Conclusion

- Coadministration with DRV/COBI or DRV + rtv demonstrated increased dabigatran exposure, indicating 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 curve from zero to infinity; BMI, body mass index; CI, confidence interval; COBI, cobicistat; C_{max}, maximum plasma concentration; CV, coefficient of variation; DRV, darunavir; FDC, fixed-dose combination; HIV-1, human immunodeficiency virus–1; LSM, least square mean; P-gp, p-glycoprotein; PI, protease inhibitor; PK, pharmacokinetic; rtv, ritonavir; SD, standard deviation; TEAE, treatment-emergent adverse event; t_{max}, time to maximum plasma concentration.

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