Rifabutin (RBT) Decreases Cabotegravir (CAB) Exposure Following Oral Co-administration

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Cabotegravir

- CAB is an HIV integrase strand transfer inhibitor (INSTI) in development as a long-acting (LA) injectable formulation
  - Treatment – in combination with rilpivirine LA
  - Prevention – as monotherapy
- CAB 30 mg oral dose selected as oral safety lead-in for CAB LA
- Drug-drug interaction (DDI) studies have been conducted with oral CAB to support co-administration of other agents with CAB LA

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Background

- CAB may need to be co-administered with antimycobacterial agents, especially in regions where HIV/TB co-infection is prevalent
- Significant interaction between oral CAB and rifampin (RIF) limits co-administration[1]
- Rifabutin (RBT) is an alternative antimycobacterial agent for tuberculosis treatment
  - RBT is chemically related to RIF and considered a weaker enzyme inducer of UGTs and CYP3A compared with RIF
- This study evaluated the effect of RBT on the pharmacokinetics (PK) of oral CAB in healthy participants

1. Ford et al. *Antimicrob Agents Chemother*. 2017;61:00487-17.

Rifabutin DDIs With Integrase Inhibitors

- CAB is metabolized primarily by UGT1A1, with minor contribution by UGT1A9 and with minimal victim or perpetrator DDI liability

Integrase Inhibitor	Metabolic Pathway	Impact of Rifabutin on INI PK		Recommendation
		AUC GLSM Ratio (90% CI)	Cmin/C12h GLSM Ratio (90% CI)	
Raltegravir 400 mg BID[1]	**UGT1A1**	1.19 (0.86, 1.63)	0.80 (0.68, 0.94)	No label information
Dolutegravir 50 mg QD[2]	**UGT1A1**, CYP3A	0.95 (0.82, 1.10)	0.70 (0.57, 0.87)	Co-administer without dose adjustment
Elvitegravir 150 mg QD[3]	**CYP3A**, UGT1A1/3	0.79 (0.74, 0.85)	0.33 (0.27, 0.40)	Co-administration is not recommended
Bictegravir 75 mg QD[4]	**CYP3A, UGT1A1**	0.62 (0.53, 0.72)	0.44 (0.37, 0.52)	

1. Brainard et al. *J Clin Pharmacol*. 2011;51:943-950. **2.** Dooley et al. *JAIDS*. 2013;62:21-27.
3. GENVOYA/STRIBILD product information, 11/2017;8/2017. **4.** BIKTARVY product information, 2/2018.

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Study Design

- Phase I, single-center, open-label, fixed-sequence cross-over
- 15 healthy participants were enrolled to ensure that 12 completed
  - Sample size was determined on the basis of known intrasubject variability and likely dropout rate

Period 1 Days 1-14	Period 2 Days 15-28	Follow-up
CAB 30 mg once daily for 14 days	CAB 30 mg once daily + RBT 300 mg once daily for 14 days	(10-14 days post dose)

PK sampling
Period 1: pre-dose on D13 and pre-dose,1,2,3,4,8,12, and 24 h post-dose on D14.
Period 2: pre-dose on D26, D27 and pre-dose,1,2,3,4,8,12, and 24 h post-dose on D28.

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Participant Demographics

Demographics	Overall (N=15)
Sex, n (%)	
Male	15 (100)
Age, mean (SD), years	43.7 (10.51)
Weight, mean (SD), kg	83.78 (12.310)
Ethnicity, n (%)	
Not Hispanic or Latino	15 (100)
Race, n (%)	
Asian – Central/South Asian Heritage	1 (7)
White – White/Caucasian/European	14 (93)

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Participant Disposition

	CAB 30 mg	CAB 30 mg + RBT 300 mg	Overall
Enrolled, N	15	14	15
Completed as planned, n (%)	14 (93)	12 (86)	12 (80)
Prematurely discontinued for any reason, n (%)	1 (7)	2 (14)	3 (20)
Withdrawn for AE, n (%)	0	2 (14)	2 (13)
Participant reached protocol-defined stopping criteria	1 (7%)	0	1 (7)

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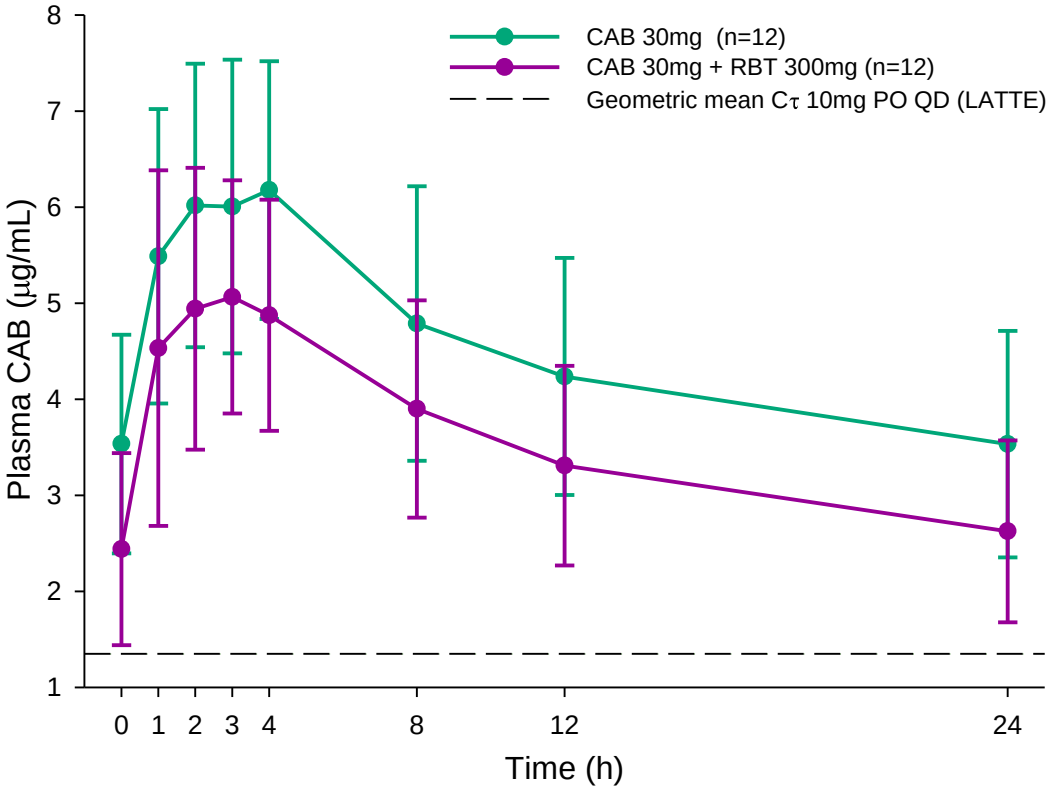
PK Results

Mean (SD) Plasma CAB Following Oral Administration With and Without Rifabutin



Summary of CAB PK Parameters and Treatment Comparisons

Plasma CAB parameter	Treatment geometric mean (95% CI)		Treatment comparison CAB + RBT/ CAB GLSM ratio (90% CI)
	CAB (n=12)	CAB + RBT (n=12)	
AUC(0-τ) (µg•h/mL)	104 (87.1, 124)	81.7 (67.9, 98.4)	0.79 (0.74, 0.83)
Cmax (µg/mL)	6.36 (5.45, 7.42)	5.25 (4.51, 6.11)	0.83 (0.76, 0.90)
Cτ (µg/mL)	3.36 (2.72, 4.15)	2.48 (1.98, 3.10)	0.74 (0.70, 0.78)
CL/F (L/h)	0.29 (0.24, 0.34)	0.37 (0.31, 0.44)	1.27 (1.20, 1.35)

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Safety Results

- Eleven participants reported 24 adverse events (AEs)
  - Most AEs were Grade 1 severity and occurred during co-administration
- No drug-related AEs were reported during CAB-only administration

Preferred term, n (%)	CAB 30 mg (N=15)	CAB 30 mg + RBT 300 mg (N=14)	Follow-up phase (N=15)
Participants with any AEs	1 (7)	7 (50)	6 (40)
Participants with any drug-related AEs	0	1 (7)	2 (13)
Leukopenia	0	1 (7)	1 (7)
Neutropenia	0	1 (7)	1 (7)
Alanine aminotransferase increased	0	1 (7)	0

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Safety Results (cont)

- A drug-related SAE was reported during follow-up
  - During CAB + RBT co-administration, 1 participant had an asymptomatic increase in ALT (grade 1) that fluctuated until reaching a peak ALT elevation (grade 3) with a corresponding elevation in direct bilirubin (grade 1) with normal total bilirubin
  - Peak ALT elevation occurred approximately 3 weeks after cessation of CAB + RBT with resolution 44 days after onset; hepatic steatosis was observed on ultrasound
- 3 participants developed AEs unrelated to study drug resulting in premature study drug withdrawal
  - 1 met protocol-defined liver stopping criteria during CAB-only administration – attributed to strenuous exercise by the investigator
  - 1 developed food poisoning and another participant developed a viral illness, both during CAB + RBT administration

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Conclusions

- Observed moderate reduction in plasma CAB exposure by RBT is not considered clinically relevant with respect to oral CAB
  - Concentrations remained above levels associated with durable suppression of HIV infection in phase II studies[1]
  - RBT modestly increased CAB oral clearance by 27% following repeat dose co-administration and reduced CAB AUC(0-τ), Cmax, and Cτ by 21%, 17%, and 26%, respectively
- A 27% increase in CL does not preclude co-administration of RBT with CAB LA
  - Simulations will inform strategies for CAB LA combination therapy and alternative dosing schedules with RBT

1. Margolis et al. *Lancet Infect Dis*. 2015;15:1145-1155.

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