Rifampin (RIF) Decreases Cabotegravir (CAB) Exposure Following Oral Coadministration

SL Ford,[1] K Sutton,[2] Y Lou,[1] J Zhang,[1] A Tenorio,[2] C Trezza,[2] P Patel,[2] W Spreen[2]

[1]PAREXEL International, Research Triangle Park, NC; [2]ViiV Healthcare, Research Triangle Park, NC

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; June 8-10, 2016; Washington, DC

Introduction

- CAB is an HIV integrase inhibitor (INI) in development as a long-acting (LA) injectable formulation for
  - Treatment—in combination with rilpivirine LA
  - Prevention—as monotherapy
- CAB 30 mg oral dose was selected as the oral safety lead-in for CAB LA and for oral drug-drug interaction (DDI) studies
- DDI studies with oral CAB have been conducted to support coadministration of other agents with CAB LA

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Introduction (cont)

- Potential need to coadminister antimycobacterial agents with CAB, particularly in regions where HIV and tuberculosis (TB) infections are highly endemic
- Treatment of TB with RIF is limited by its significant drug interaction liability as an inducer of UGT and CYP enzymes
- This study was undertaken to evaluate the effect of RIF on the pharmacokinetics (PK) of oral CAB in healthy subjects

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Cabotegravir Metabolism

- CAB is metabolized primarily by UGT1A1, with minor contribution by UGT1A9[1] and with minimal victim or perpetrator DDI liability
- Coadministration of other INIs with RIF

Integrase Inhibitor	Metabolic Pathway	RIF Impact on INI AUC	Recommendation
Raltegravir[2]	**UGT1A1**	↓40%	↑RAL from 400 mg to 800 mg BID with RIF
Dolutegravir[3]	**UGT1A1**, CYP3A	↓54%	↑DTG 50 mg from QD to BID with RIF (INI-naive patients)
Elvitegravir[4]	**CYP3A**, UGT1A1/3	NA	Coadministration with RIF not recommended

1. Xue et al. Clin Pharm 2016; Washington, DC. Poster P_36. **2.** ISENTRESS product information,15FEB15. **3.**TIVICAY product information, 22APR16. **4.** VITEKTA/STRIBILD product information, 27JUL15/19FEB16.

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Study Design

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

Period 1 Day 1–Day 7	Period 2 Days 8–20	Period 3 Days 21–28
Single dose CAB 30 mg (Day 1)	RIF 600 mg once daily for 13 days (Days 8–20)	Single dose CAB 30 mg (Day 21) + RIF 600 mg QD for 8 days (Days 21–28)

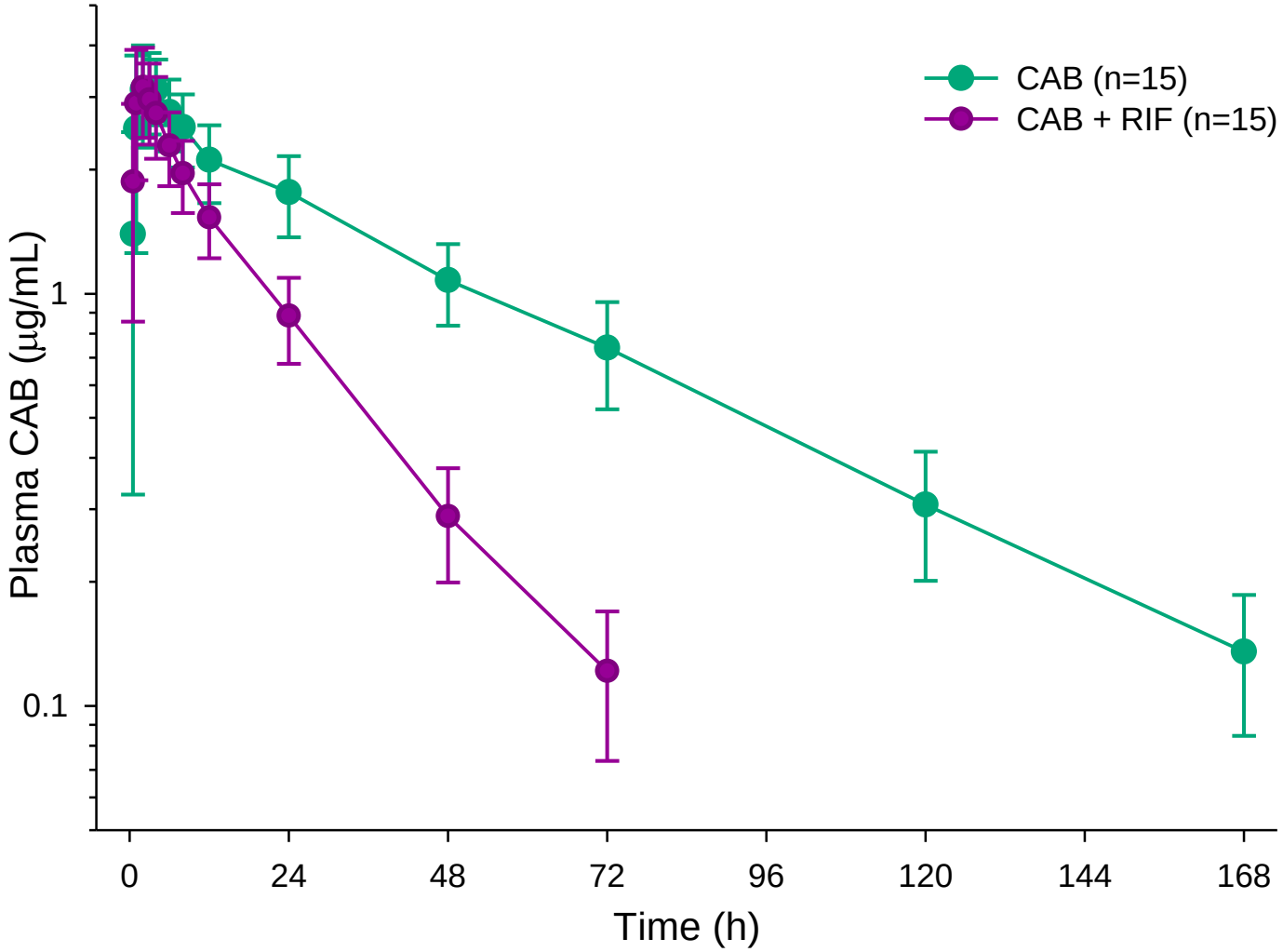
Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Subject Demography and Disposition

Demographics	Overall
Number of subjects completed as planned, n (%)	15 (100)
Sex, n (%)	
Female	5 (33)
Male	10 (67)
BMI, mean (SD), kg/m^2	26.71 (3.6)
Height, mean (SD), cm	172.41 (7.0)
Weight, mean (SD), kg	79.63 (13)
Race, n (%)	
African American/African Heritage	3 (20)
White/Caucasian/European Heritage	12 (80)

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Mean (SD) Plasma CAB Conc-Time Profiles Following Administration With and Without RIF



Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Summary of Plasma CAB PK Parameters and Treatment Comparisons

Plasma CAB Parameter	Treatment Geometric Mean (95% CI)		Treatment Comparison CAB + RIF: CAB (Test:Reference) GLSM Ratio (90% CI)
	CAB (Reference) (n=15)	CAB + RIF (Test) (n=15)	
AUC(0-∞), μg•h/mL	146 (128, 167)	59.7 (52.8, 67.5)	0.41 (0.36, 0.46)
Cmax, μg/mL	3.61 (3.28, 3.96)	3.39 (3.05, 3.76)	0.94 (0.87, 1.02)
CL/F, L/h	0.205 (0.180, 0.234)	0.502 (0.444, 0.568)	2.4 (2.2, 2.8)
$t_{1/2}$, h	38.5 (35.7, 41.6)	16.4 (14.7, 18.2)	0.43 (0.39, 0.46)

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Safety Results

Overall summary of all subjects with drug-related adverse events

- No SAEs were observed during the study

Event	CAB	RIF 600 mg QD	CAB + RIF	Overall
	n (%)	n (%)	n (%)	n (%)
Any AE	3 (20)	15 (100)	1 (7)	15 (100)
Any AE related to IP	1 (7)	15 (100)	0	15 (100)
Chromaturia	0	15 (100)	0	15 (100)
Decreased appetite	0	2 (13)	0	2 (13)
Headache	1 (7)	1 (7)	0	2 (13)
Fatigue	0	1 (7)	0	1 (7)

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Conclusions

- Coadministration of steady-state RIF 600 mg with single-dose CAB 30 mg increased CAB oral clearance 2.4-fold and decreased CAB AUC(0-∞) by 59% (CAB Cmax was unaffected)
- CAB administered alone or in combination with steady-state RIF was tolerated in the study with no serious AEs or grade 3 or 4 laboratory abnormalities reported

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Recommendations

- Coadministration of RIF with oral CAB 30 mg once daily is not recommended
- Coadministration of RIF with CAB LA is not recommended without further study
  - Increased CL on popPK modeling and simulation may aid in understanding RIF impact on CAB LA

Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.

Acknowledgments

- Study participants who endured 21 days of RIF
- Staff at Quintiles, Kansas City, MO
- CAB development team
- Steve Piscitelli
- Elizabeth Gould