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Evaluation of Relationships Between *UGT1A1* Genotypes and Cabotegravir Long-Acting Injection Pharmacokinetics Among HIV-Infected Subjects in the LATTE-2 Study

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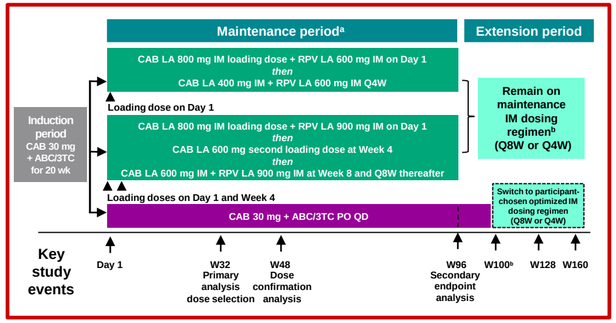
Introduction

- Cabotegravir (CAB), an HIV integrase inhibitor primarily metabolized by UGT1A1, is in development as an oral tablet and long-acting (LA) intramuscular (IM) injection for the treatment and prevention of HIV infection. CAB LA has a prolonged absorption phase, typical of flip-flop pharmacokinetics (PK), which yields prolonged drug exposure compared with oral administration
- Genetic variation in *UGT1A1* affects enzymatic activity, impacting drug exposure.[1-4] A previous analysis demonstrated that *UGT1A1* genotypes conferring poor metabolizer status were significantly associated with steady-state oral CAB PK parameters, with ~1.5-, 1.4-, and 1.3-fold increases in mean C_t, AUC, and C_{max}, respectively, in healthy and HIV-infected subjects with low versus normal genetically predicted UGT1A1 activity. These increases are not considered clinically relevant[5]
- The present analysis assessed the impact of *UGT1A1* genotypes on CAB PK in HIV-infected subjects receiving oral and LA IM CAB in the LATTE-2 study (Figure 1)
  - DNA from 215 HIV-infected subjects with PGx consent who received CAB LA every 4 weeks (Q4W) or every 8 weeks (Q8W) in LATTE-2 was genotyped
  - *UGT1A1* variants (*6, *28, *36, and *37) were used to classify subjects with genetically predicted low (n=33), reduced (n=100), or normal (n=82) UGT1A1 enzyme activity
  - A linear regression analysis, adjusting for significant nongenetic covariates, was used to determine if genetically predicted UGT1A1 activity had an effect on CAB LA PK parameters at Weeks 32 and 48
  - The effect of *UGT1A1* genotypes on CAB LA PK will be also be evaluated in a population PK model following completion of phase III studies

Figure 1. LATTE-2 (NCT02120352) Study Design



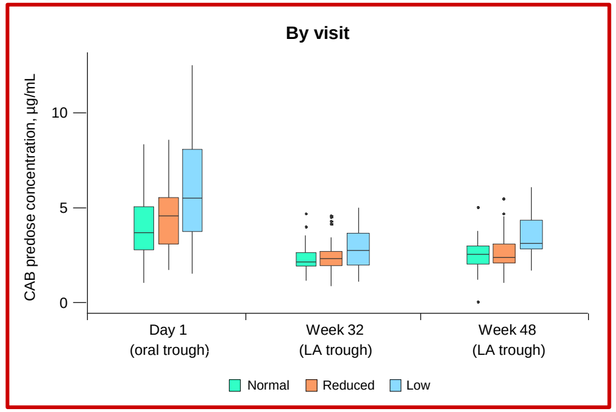
ABC/3TC, abacavir/lamivudine; CAB, cabotegravir; IM, intramuscular; LA, long-acting; PO, oral; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine. [a]Participants who withdraw after receiving at least 1 IM dose will be followed on study via long-term follow-up period with quarterly visits for 52 weeks. [b]If eligible.

Table. Effects of Genetically Predicted UGT1A1 Activity[a] on CAB LA PK

Parameter	Covariate	Study week	Analysis population, N	*P* value	Parameter by genetically predicted UGT1A1 activity status, mean (min, max)			
					Normal	Reduced	Low	Fold change[b]
C_t, ug/mL	Dosing regimen	32	164	0.0123	n=67	n=74	n=23	1.22
	Weight				1.85 (0.5, 4.7)	2.06 (0.27, 4.58)	2.25 (0.21, 5.01)	
		48	159	0.0037	n=61	n=75	n=23	1.24
					1.88 (0, 5.13)	2.19 (0.19, 5.49)	2.32 (0, 6.11)	
$AUC_{0\text{-}t}$, h·ug/mL	Dosing regimen	32	215	0.0201	n=82	n=100	n=33	1.20
	Weight				2571 (1020, 6392)	2773 (609, 11313)	3082 (978, 11092)	
		48	212	0.0162	n=81	n=99	n=32	1.16
					2696 (323, 9755)	2762 (277, 9288)	3133 (1230, 6256)	
C_{max}, ug/mL	Weight	32	215	0.0310	n=82	n=100	n=33	1.22
					3.68 (0.91, 9.66)	3.99 (1.08, 21.4)	4.49 (1.10, 11.7)	
		48	212	0.0047	n=81	n=99	n=32	1.18
					3.53 (1.56, 8.08)	3.78 (1.03, 10.5)	4.16 (1.66, 11.5)	

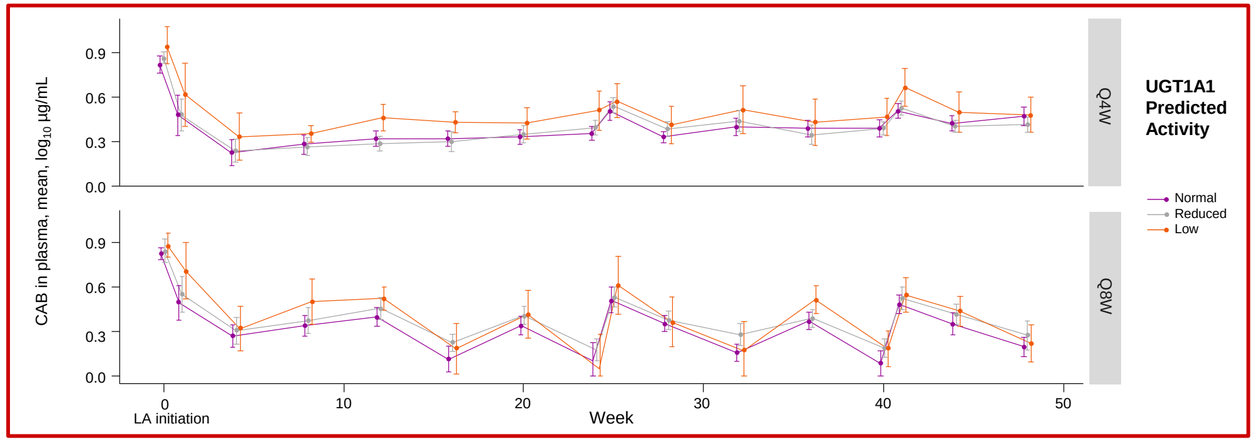
$AUC_{0\text{-}t}$, area under the concentration-time curve from 0 h to last quantifiable measurement; C_t, concentration at the end of dosing interval; C_{max}, maximum observed plasma concentration. [a]Definition for genetically predicted UGT1A1 activity: carriage of 2 copies of *28 (TA7), *37 (TA8), and/or *6 allele for "low," 1 copy for "reduced," and 0 for "normal," respectively. [b]Fold change in mean PK parameter values between patients with low vs. normal predicted UGT1A1 activity.

Figure 3. Oral Versus LA CAB Trough Overall Concentrations



CAB, cabotegravir; LA, long acting.

Figure 2. Mean (95% CI) CAB LA Concentration-Time Profile by Treatment and UGT1A1 Predicted Activity Status



CAB, cabotegravir; CI, confidence interval; LA, long acting; Q4W, every 4 weeks; Q8W, every 8 weeks.

Discussion

- Genetically predicted UGT1A1 activity was statistically associated with CAB LA C_t, $AUC_{0\text{-}t}$, and C_{max} (P<0.05) at Weeks 32 and 48
- Nongenetic covariates of age, weight, dosing regimen, body mass index, and sex were considered. Of them, dosing regimen and weight were significantly (P<0.05) associated with CAB LA C_t, $AUC_{0\text{-}t}$, and C_{max}, respectively, and included in the final model for analysis (Table). Those covariates remained significant after accounting for UGT1A1 predicted activity status with the exception of "weight" for the C_t and $AUC_{0\text{-}t}$ at Week 32
- Mean LA PK parameters increased approximately 1.2-fold in subjects with low versus normal genetically predicted UGT1A1 activity (Table)
- The impact of *UGT1A1* genotypes on CAB LA PK parameters was smaller than that observed for oral CAB dosing (Figure 3), which may indicate that the LA sustained drug delivery can mask/blunt the impact of the poor enzymatic activity

Conclusions

- *UGT1A1* reduced-function polymorphisms modestly increased CAB PK parameters in HIV-infected patients who received CAB by oral or IM administration
- The approximate 1.2-fold difference in mean PK parameter values between patients with low versus normal predicted UGT1A1 activity was lower than that observed with oral CAB and is not considered to have a clinically relevant impact
- Based on the accumulated safety profile of CAB, individuals with *UGT1A1* reduced-function polymorphisms do not require dose adjustment for either oral or LA CAB administration

Acknowledgments

This study was funded by ViiV Healthcare. The authors would like to thank the investigators and patients who made this study possible. We would also like to acknowledge Joseph Piscitelli, PharmD Candidate, University of North Carolina School of Pharmacy, for his contributions to the poster. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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