

Poster Sessions – Abstract P052

The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects

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Introduction: Dolutegravir (DTG) is an HIV integrase strand transfer inhibitor approved for use in combination with other antiretrovirals for the treatment of HIV-infection in adults and adolescents. Metformin is a drug frequently used in diabetic HIV-infected patients, which requires titration to optimize dosing. *In vitro*, DTG inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE 1) which are known to be involved in the disposition of metformin. The objective of this study was to assess the drug interaction between DTG and metformin.

Materials and Methods: This was an open-label, parallel-group, three-period crossover study in healthy adult subjects. Eligible subjects were enrolled into one of the two treatment cohorts (15 subjects/cohort). Subjects received metformin 500 mg q12h for 5 days in Period 1; metformin 500 mg q12h plus DTG 50 mg q24h (Cohort 1) or 50 mg q12h (Cohort 2) for 7 days in Period 2; and metformin 500 mg q12h for 10 days in Period 3. There were no washout periods between treatments. All doses of study drug were taken with a moderate-fat meal. Serial plasma PK samples and safety assessments were obtained throughout the study. Non-compartmental PK analysis was performed and geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) were generated by the mixed effect model for within-subject treatment comparisons for each cohort.

Results: Fourteen and thirteen subjects completed study in Cohort 1 and Cohort 2, respectively. Plasma exposures of metformin were significantly increased when co-administered with DTG (Table 1).

There were no apparent changes in metformin half-life and tmax. Increased metformin plasma exposure returned to normal levels observed in Period 1 after DTG was discontinued in Period 3. No Grade 3 or 4 adverse events (AEs), deaths or serious AEs were reported during the study. Most frequently reported drug-related AEs were headache (9), loose stools (8), and nausea (7). All AEs were mild or Grade 1 with the exception of one Grade 2 headache.

Conclusions: Co-administration of DTG and metformin was well tolerated, yet significantly increased metformin plasma exposure; effects were DTG dose dependent. Though metformin has a wide therapeutic index and alone is not associated with hypoglycemia, close monitoring is recommended when co-administering metformin and DTG. Dose adjustments of metformin may be considered.

Table 1. Statistical comparison of metformin PK parameters with and without dolutegravir

Plasma Metformin PK Parameter	GLS mean	Metformin + DTG (Period 2)	GLS mean ratio (90% CI)
	Metformin Alone (Period 1)		Metformin + DTG vs. Metformin Alone
Cohort 1 (DTG 50 mg QD)	n = 15	n = 14	
Cmax (µg/mL)	0.932	1.55	1.66 (1.53, 1.81)
AUC(0-τ) (hr*µg/mL)	6.83	12.2	1.79 (1.65, 1.93)
Cohort 2 (DTG 50 mg BID)	n = 15	n = 14	
Cmax (µg/mL)	0.845	1.878	2.11 (1.91, 2.33)
AUC(0-τ) (hr*µg/mL)	6.49	15.9	2.45 (2.25, 2.66)

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