1388 Pharmacokinetics of Cabotegravir in Subjects With Moderate Hepatic Impairment

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Abstract

Background: Cabotegravir (CAB) is an integrase inhibitor in phase 3 clinical trials for the treatment and prevention of HIV. CAB undergoes hepatic metabolism primarily via UGT1A1; thus hepatic impairment has the potential to affect CAB exposure.

Methods: This was a multi-center, single-dose, open-label, parallel group study to evaluate the effect of moderate hepatic impairment on the pharmacokinetics (PK) and safety of CAB. Adults with moderate hepatic impairment as determined by Child-Pugh classification score of 7-9 (n=8) and matched healthy control subjects (n=8) were enrolled. Control subjects were matched for gender, age (±10 years), and body mass index (BMI) (±25%). Subjects received oral CAB 30 mg as a single dose in the fasted state followed by serial PK sampling for 168 hours. CAB unbound concentrations at 2 and 24 hours after dosing were determined by equilibrium dialysis. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios (hepatic impaired group/control group) and 90% confidence intervals (CI) were generated.

Results: Sixteen subjects completed study; 12 (75%) male, mean age 59 years (range: 51-67), mean BMI 29 kg/m^2 (range: 21-37), and total Child-Pugh score in range of 7-9. CAB PK parameters were similar between subjects with moderate hepatic impairment and matched healthy subjects. The GLS mean ratios (90% CI) for AUC(0-∞), Cmax, C24, CL/F, and t1/2 were 0.73 (0.50, 1.06), 0.69 (0.51, 0.93), 0.73 (0.53, 1.02), 1.38 (0.95, 2.01), and 0.82 (0.65, 1.04), respectively. Although highly protein bound, the unbound fraction of CAB was increased in subjects with moderate hepatic impairment relative to healthy subjects with GLS mean ratio (90% CI) of 2.14 (1.57, 2.90) at 2 hours post dose and 1.90 (1.14, 3.18) at 24 hours post dose; this was associated with lower serum albumin concentrations and was not considered clinically significant. All adverse events (AEs) were reported as mild (grade 1) to moderate (grade 2) in severity and no serious AEs were reported.

Conclusion: Plasma exposures of CAB in subjects with moderate hepatic impairment were similar to those in healthy subjects. No dose adjustment of CAB is required for subjects with mild to moderate hepatic impairment.

Introduction

- Cabotegravir (CAB) is a potent integrase strand transfer inhibitor in phase III clinical development for the treatment and prevention of HIV-1 infection
- CAB is primarily metabolized by UGT1A1 and UGT1A9[1] and is extensively bound to plasma proteins with an unbound fraction of <1%
- Liver dysfunction is common in HIV-infected and hepatitis C–coinfected patient populations; therefore, the effect of hepatic impairment (HI) on CAB exposure was characterized to provide dosing recommendations in HI
- This study was conducted to evaluate the PK of CAB in subjects with moderate HI compared with a group of matched healthy subjects who were seronegative

Methods

- An open-label, parallel-group, single-dose, adaptive study (NCT02354950) was conducted in 16 adults; 8 with moderate HI (Child-Pugh classification score of 7-9) and 8 healthy controls matched for gender, age (±10 years), and BMI (±25%; Table 1)
- All subjects received a single oral dose of CAB 30 mg in the fasted state and underwent serial PK sampling through 168 hours to determine total plasma CAB concentrations
- CAB fraction unbound (FU %) was determined at 2 and 24 hours post dose by equilibrium dialysis method
- Non-compartmental PK analysis was performed. Geometric least squares (GLS) mean ratios (moderate HI/healthy control group) and associated 90% CIs were generated for PK parameters
- A cohort of subjects with mild HI was planned if the AUC of subjects with moderate HI was >2 fold that of matched healthy subjects
- Safety and tolerability were assessed during the study and included physical exam, vital signs, ECGs, hematology, and clinical chemistry

Table 1. Study Demographics and Disposition

Demographics	Mod HI (n=8)	Healthy (n=8)	Total (N=16)
Females:males, n (%)	2:6 (25:75)	2:6 (25:75)	4:12 (25:75)
Age, mean (SD), y	60.3 (3.20)	56.9 (6.17)	58.6 (5.06)
BMI, mean (SD), kg/m^2	29.3 (3.78)	29.2 (4.17)	29.2 (3.85)
African American/African heritage, n (%)	2 (25)	2 (25)	4 (25)
White (White/Caucasian/ European heritage), n (%)	6 (75)	6 (75)	12 (75)
Child-Pugh total score, n (%)			
7	3 (37.5)	-	-
8	3 (37.5)		
9	2 (25.0)		

Healthy, matched healthy controls; mod HI, moderate hepatic impairment; SD, standard deviation.

Results

- Demographics of study subjects were well matched between cohorts
- Total plasma CAB AUC(0-∞) and Cmax were approximately 27% and 31% lower, respectively, in moderate HI subjects compared with matched healthy subjects (Table 2; Figure)
- Mean CAB unbound fraction (%) in moderate HI subjects was ~90% to 114% higher than in healthy subjects (Table 2)
- Since AUC(0-∞) of CAB was not increased >2 fold in moderate HI subjects, no analysis of the impact of mild HI on CAB PK was conducted
- All AEs reported were mild (grade 1) or moderate (grade 2) in severity (Table 3). There were no deaths or serious AEs reported, and no subjects discontinued from the study because of AEs
- No clinically significant trends in clinical laboratory values, vital signs, or ECG values were observed during the study

Figure. Mean (±SD) Total CAB Plasma Pharmacokinetic Profiles

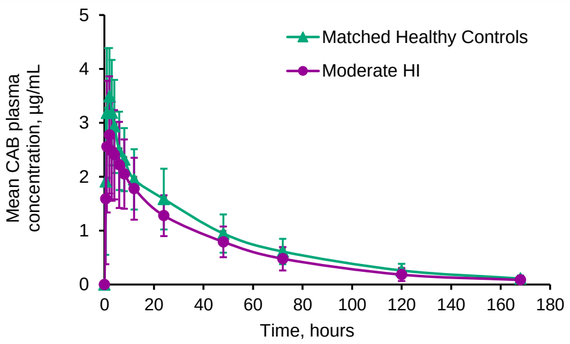

Table 2. Summary of Select CAB PK Parameters by Cohort

PK parameter	Mod HI (n=8)[a]	Healthy (n=8)[a]	GLS mean ratio mod HI vs healthy (n=8)[b]
AUC(0-∞), h*µg/mL	102 (37.3)	127 (36.2)	0.73 (0.50, 1.06)
AUC(0-t), h*µg/mL	98.2 (36.2)	121 (35.4)	0.73 (0.51, 1.05)
Cmax, µg/mL	2.70 (41.1)	3.55 (24.3)	0.69 (0.51, 0.93)
C24, µg/mL	1.23 (30.8)	1.50 (35.6)	0.73 (0.53, 1.02)
t1/2, h	30.8 (32.2)	37.2 (13.1)	0.82 (0.65, 1.04)
CL/F, L/h	0.30 (37.3)	0.24 (36.2)	1.38 (0.95, 2.01)
CU2H, µg/mL[c,d]	0.0095 (69)	0.0059 (38)	1.40 (0.80, 2.46)
CU24H, µg/mL[c,d]	0.0050 (63)	0.0026 (40)	1.55 (0.82, 2.94)
FU2H, %[d]	0.307 (47.6)	0.157 (30.5)	2.14 (1.57, 2.90)
FU24H, %[d]	0.322 (66.6)	0.166 (23.9)	1.90 (1.14, 3.18)

CU2H, unbound concentration at 2 h; CU24H, unbound concentration at 24 h; FU2H, unbound fraction at 2 h; FU24H, unbound fraction at 24 h; GLS, geometric least squares; healthy, matched healthy controls; mod HI, moderate hepatic impairment. [a]Geometric mean (%CVb), unless otherwise specified. [b]GLS mean ratio (90% confidence interval). [c]Arithmetic mean (%CV). [d]Sample size, n=7.

Discussion

- CAB was readily absorbed with maximum concentrations achieved 2 hours post dose
- Moderate HI subjects demonstrated higher unbound CAB concentrations, resulting in higher clearance, shorter t1/2, and lower plasma exposures compared with matched healthy subjects
- Lower albumin levels may explain the higher CAB unbound fraction observed in HI subjects. Changes in intrinsic clearance of CAB are likely minimal because UGT enzymes are high-capacity enzymes and less likely to be altered in moderate HI
- The reduced total plasma CAB exposures in moderate HI subjects were not considered clinically relevant

Table 3. Safety Summary of CAB by Cohort

All adverse events (safety population), n (%)	Mod HI (n=8)	Healthy (n=8)	Overall (N=16)
Subjects with any AE(s)	2 (25)	3 (38)	5 (31)
Folliculitis	1 (13)	0	1 (6)
Gastroenteritis	1 (13)	0	1 (6)
Upper respiratory tract infection[a]	0	1 (13)	1 (6)
Constipation[a]	1 (13)	0	1 (6)
Blood pressure increased[a]	0	1 (13)	1 (6)
Back pain	0	1 (13)	1 (6)
Headache[a]	0	1 (13)	1 (6)
Papule	1 (13)	0	1 (6)

Healthy, matched healthy controls; mod HI, moderate hepatic impairment. [a]Considered drug related by study investigator.

Conclusions

- The impact of moderate HI on CAB PK was not considered clinically relevant
- CAB can be administered without dose adjustment in subjects with mild to moderate HI

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Reference: 1. Bowers GD, Culp A, Reese MJ et al. Disposition and metabolism of cabotegravir: a comparison of biotransformation and excretion between different species and routes of administration in humans. *Xenobiotica.* 2016;46(2):147-62.