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Pharmacokinetics of Cabotegravir in Subjects With Severe Renal 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 glucuronidation via UGT1A1 with <1% renal elimination of unchanged CAB. Renal impairment may affect PK of drugs that are primarily metabolized or secreted in bile, thus impact of renal impairment on CAB pharmacokinetics was evaluated.

Methods: This was a multi-center, single-dose study of oral CAB 30 mg administered to subjects with severe renal impairment (creatinine clearance [CLcr] <30 mL/min; not on renal replacement therapy) and to healthy controls (CLcr ≥90 mL/min) matched for gender, age (±10 years), and body mass index (BMI) (±25%) (8 per group). Serial PK for plasma CAB concentrations were collected through 168 hours post dose and unbound CAB concentrations determined at 2 and 24 hours post dose. Non-compartmental PK analysis was performed; geometric least squares (GLS) mean ratios and 90% confidence intervals (CI) were generated.

Results: Sixteen subjects completed study; 12 (75%) male, mean age 54 years (range: 35-69), mean BMI 28 kg/m^2 (range: 24-35), and mean CLcr 22 mL/min (range: 17-29) and 121 mL/min (range: 95-162) for renal impaired and healthy subjects, respectively. CAB PK parameters were similar between severe renal impairment and healthy subjects. Based on preliminary PK, GLS mean ratios (90% CI) for AUC(0-∞), Cmax, C24, CL/F, and t1/2 were 0.973 (0.835, 1.135), 1.01 (0.865, 1.168), 1.02 (0.868, 1.202), 1.03 (0.881, 1.198), and 0.93 (0.831, 1.041), respectively. Although highly protein bound, the unbound fraction was higher in subjects with severe renal impairment with GLS mean ratio (90%CI) of 1.31 (0.843, 2.029) at 2h and 1.51 (1.191, 1.923) at 24h post dose. One renal impairment subject developed grade 3 lipase elevation considered drug-related by investigator, otherwise all reported adverse events (AE) were grade 1 in severity with no serious AEs reported.

Conclusion: Plasma CAB exposures in subjects with severe renal impairment were similar to healthy subjects; therefore, no dose adjustment of CAB is required in renal impairment. Although no data are available, CAB PK is not expected to be affected in subjects undergoing dialysis given CAB's non-renal clearance and high plasma protein binding (~99%).

Introduction

- Cabotegravir (CAB) is an integrase strand transfer inhibitor currently in phase 3 clinical studies for the treatment and prevention of HIV infection with both oral and long-acting injectable formulations
- CAB is predominantly metabolized by UGT1A1 with <1% of unchanged CAB undergoing renal elimination
- Renal impairment can affect drug absorption, hepatic/gut drug metabolism, plasma protein binding, and drug transport; therefore, this study evaluated the pharmacokinetics (PK) of CAB in subjects with severe renal impairment compared with matched healthy subjects

Methods

- Phase I, two-center, open-label, single-dose, parallel-design study was conducted in 16 adults; 8 with severe renal impairment and 8 healthy controls matched for gender, age (±10 years), and body mass index (BMI; ±25%)

Table 1. Study Design

Sample size	Renal function	CLcr*	Treatment
8	Severe renal impairment	<30 mL/min	Oral CAB 30 mg
8	Normal renal function	≥90 mL/min	Oral CAB 30 mg

*CLcr was determined at screening by 24-hour urine collection.

- All subjects received a single oral dose of CAB 30 mg in the fasted state and underwent serial PK collection through 168 hours to determine total plasma CAB concentrations
- Non-compartmental PK analysis was performed. Geometric least squares (GLS) mean ratios (severe renal impairment/healthy control group) and associated 90% confidence intervals (CIs) were generated for PK parameters using ANCOVA, with cohort and gender as fixed effects and age and BMI as continuous covariates
- CAB fraction unbound (FU%) was determined at 2 and 24 hours post dose using an equilibrium dialysis method
- Safety and tolerability were assessed during the study and included physical exam, vital signs, ECGs, hematology, and clinical chemistry

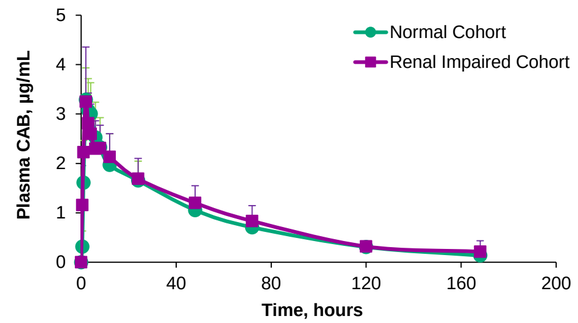
Table 2. Subject Demographics

	Renal impaired cohort (N=8)	Normal cohort (N=8)
Male, n (%)	6 (75)	6 (75)
Age, mean ± SD, years	55.6 ± 11.12	52.3 ± 11.27
BMI, mean ± SD, kg/m^2	28.51 ± 3.424	28.13 ± 3.804
White, n (%)	5 (63)	6 (75)
Creatinine clearance, mean ± SD, mL/min	22.1 ± 3.83	121.3 ± 21.66

Results

- Subject demographics were well matched between groups
- Total plasma CAB exposures were similar between severe renal impairment subjects and matched healthy controls based on the results of statistical comparisons
- Plasma PK parameters Cmax, AUC(0-∞), AUC(0-t), and t1/2 were similar between renal impaired and normal cohort

Figure. Mean (SD) Plasma CAB Concentration–Time Profile



- Unbound CAB fraction (%) in renally impaired cohort was 31% to 51% higher than those in healthy subjects at 2 hours and 24 hours post dose

Table 3. CAB PK Parameters[a]

PK parameter, geometric mean (%CVb)	Renal impaired cohort (N=8)	Normal cohort (N=8)	LS means ratio[a] (90% CI)
AUC(0-∞), h*µg/mL	143 (23)[b]	140 (23)	0.97 (0.835, 1.135)
AUC(0-t), h*µg/mL	143 (27)	133 (23)	1.08 (0.885, 1.320)
Cmax, µg/mL	3.34 (27)	3.37 (15)	1.01 (0.865, 1.168)
C24, µg/mL	1.65 (25)	1.62 (23)	1.02 (0.868, 1.202)
t1/2, h	39.2 (16)[b]	40.5 (11)	0.93 (0.831, 1.041)
FU2H, %	0.18 (29)	0.14 (63)	1.31 (0.843, 2.029)
FU24H, %	0.17 (17)	0.11 (30)	1.51 (1.19, 1.923)
CL/F, L/h	0.21 (23)[b]	0.21 (23)	1.03 (0.881, 1.198)

[a]Ratio calculation severe renally impaired versus healthy match. [b]N=7.

Adverse Events Summary

Table 4. Adverse Events (Safety Population)

n (%)	Renal impaired cohort N=8	Normal cohort N=8	Overall N=16
Subject with any AE(s)	3 (38)	2 (25)	5 (31)
Change of bowel habit	0	1 (13)	1 (6)
Diarrhea	0	1 (13)	1 (6)
Gastrointestinal pain	1 (13)	0	1 (6)
Nausea	1 (13)	0	1 (6)
Vomiting	1 (13)	0	1 (6)
Conjunctival hemorrhage	0	1 (13)	1 (6)
Infusion-site pain	1 (13)	0	1 (6)
Lipase increased	1 (13)	0	1 (6)
Somnolence	1 (13)	0	1 (6)

- There were no deaths, serious adverse events (AEs), or study withdrawals due to AEs. All AEs were grade 1, except 1 subject with a history of elevated lipase prior to treatment who had grade 3 lipase increase

Discussion

- Severe renal impairment did not affect total plasma CAB exposures consistent with previous data, which showed that less than 1% of radiolabeled CAB dose was excreted in the urine unchanged[1]
- Increases in CAB unbound fraction of up to 50% in the renally impaired cohort were not considered clinically significant
- No data are available for subjects receiving dialysis, although, given its non-renal clearance and high plasma protein binding (~99%), this would not be expected to affect CAB PK

Conclusions

- There was no impact of severe renal impairment on CAB PK
- CAB can be administered without the need for dose adjustment in subjects with mild to severe renal impairment

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Reference: 1. Bowers HF, Culp S, 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):147-162.