PHARMACOKINETICS OF ALG-097558, A PAN-CORONAVIRUS 3CL-PRO INHIBITOR, IN RENAL AND HEPATIC IMPAIRMENT

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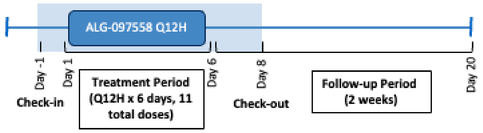
BACKGROUND

ALG-097558 is a novel, potent small molecule inhibitor of SARS-CoV-2 3-chymotrypsin like protease (3CL-Pro) that demonstrated pan-coronavirus activity and ≥3-fold more activity than nirmatrelvir in vitro. Favorable pharmacokinetics (PK) and safety data observed after dosing ALG-097558 for ≤7 days in healthy subjects support the development of ALG-097558 as an oral, ritonavir (RTV)-free treatment for COVID-19 with reduced risk of drug-drug interactions [1]. Therefore, studies were conducted to assess how hepatic and renal impairment affect ALG-097558 PK to guide dosing in populations at risk for severe COVID-19.

METHODS

The hepatic impairment (HI) Study ALG-097558-702 (NCT06568861) was a Phase 1 non-randomized, open-label, multiple dose study in participants with moderate hepatic impairment (Child Pugh Class B [score 7-9]; N=8) and in healthy participants with normal hepatic function (N=8). The renal impairment (RI) Study ALG-097558-702 (NCT06698549) was a Phase 1 non-randomized, open-label, multiple dose study in participants with severe renal impairment (BSA-adjusted eGFR <30 mL/min, not requiring dialysis; N=6) and in healthy participants with normal renal function (BSA adjusted eGFR ≥90 mL/min; N=6). The primary endpoint for these studies was plasma and urine (RI only) PK parameters in each cohort of total and unbound) ALG-097558 and the major metabolite ALG-097730.



Light blue shaded area indicates confinement to clinical research unit

Dose level (Q12H)
HI = 200 mg
RI = 300 mg

Figure 1. Study Design for HI and RI

For both studies, blood samples for PK analysis were collected on Day 1: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-first dose; Days 2-5: pre-AM dose; Day 6: predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 14 hours post-last dose; Day 7 and 8: 24, 36 and 48 hours post-last dose. For the RI study, urine samples were collected at predose, 0-6 h post-first dose on Day 1 and predose, 0-6, 6-12, 12-24, 24-36, and 36-48 h post-last dose. All samples were analyzed using LC-MS/MS. Throughout HI and RI study conduct, safety assessments (adverse events [AEs], vital signs, electrocardiograms, and laboratories) were collected and analyzed.

BASELINE CHARACTERISTICS

Baseline characteristics of Cohort 1 of both the HI and RI studies were generally representative of the HI and RI patient population, respectively.

In each study, Cohort 2 participants without HI or RI, respectively, were matched to Cohort 1 median demographics (age [± 10 kg], body weight [± 15 kg], and gender).

TABLE 1. MEDIAN DEMOGRAPHICS FOR THE HEPATIC IMPAIRMENT STUDY

	Cohort 1 (N=8)	Cohort 2 (N=8)
Age, years	63	63
Body Weight, kg	71.3	71.7
% Male (n)	37.5 (3)	37.5 (3)
Child Pugh Score (n)	7 (5) 8 (2) 9 (1)	N/A

TABLE 2. MEDIAN DEMOGRAPHICS FOR THE RENAL IMPAIRMENT STUDY

	Cohort 1 (N=6)	Cohort 2 (N=6)
Age, years	47.5	46
Body Weight, kg	77.7	77.6
% Male (n)	83.3 (5)	83.3 (5)
eGFR, mL/min (min, max)	16.75 (7.5, 25.5)	128.5 (104, 143)

RESULTS

SAFETY

- Generally well-tolerated
- Serious adverse events (SAEs) only reported in HI study: Two unrelated SAEs (Grade 3 alcoholic hepatitis and alcohol withdrawal) in Cohort 1 subject occurring after the Day 20 Follow-up visit
- One study drug discontinuation in HI study: One treatment-emergent AE (TEAE) of Grade 2 epigastric pain in Cohort 2 subject leading to discontinuation
- Majority of the TEAEs were mild or moderate
- No clinically meaningful findings in laboratory tests, electrocardiograms, vital signs, or physical examinations were observed in either study

MODERATE HEPATIC IMPAIRMENT

- Moderate HI had no clinically meaningful effect on the PK of ALG-097558
- The plasma exposures of ALG-097558 in participants with moderate HI were comparable to those in demographically-matched participants with normal hepatic function (Table 3)
- As unbound fraction of ALG-097558 was higher (0.09) in participants with HI than in healthy participants (0.05), the exposure of unbound ALG-097558 was higher in HI subjects but remained <2-fold compared to healthy participants
- There was no impact of moderate HI on ALG-097558 metabolism as the ALG-097558 to ALG-097730 molar ratio was generally similar between the two cohorts

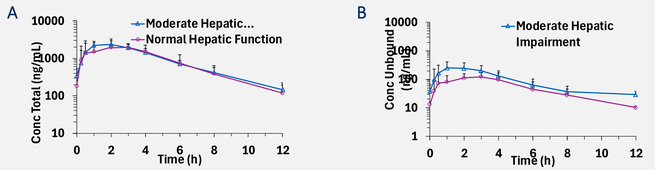


Figure 2. Mean Plasma Concentration-Time Profile of Total (A) and Unbound (B) ALG-097558 at Steady State in Participants with Moderate Hepatic Impairment vs. Normal Hepatic Function

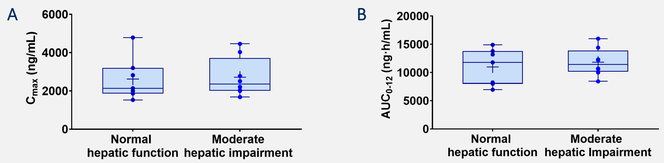


Figure 3. Mean, Median and Individual Plasma C_{max} (A) and AUC_{0-12} (B) of ALG-097558 in Participants with Normal Hepatic Function and Moderate Hepatic Impairment

SEVERE RENAL IMPAIRMENT

- Severe RI had no clinically meaningful effect on the PK of ALG-097558
- The increase in plasma exposures of ALG-097558 in participants with severe RI (worst-case scenario) was ≤1.66-fold relative to the healthy participants (Table 3)
- The increase in the exposure of unbound ALG-097558 and ALG-097730 (total and unbound) each was also <2-fold
- There was no change in mean unbound fraction of ALG-097558 or ALG-097730 between the 2 cohorts
- As expected, urinary excretion (Fe_{0-48}) of ALG-097558 and ALG-097730 was low and decreased in participants with RI (1.3%) as compared to healthy participants (4.4%)

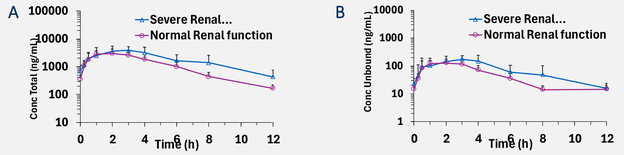


Figure 4. Mean Plasma Concentration-Time Profile of Total (A) and Unbound (B) ALG-097558 at Steady State in Participants with Severe Renal Impairment vs. Normal Renal Function

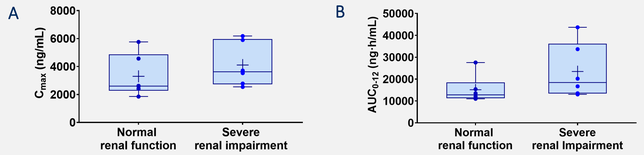


Figure 5. Mean, Median and Individual Plasma C_{max} (A) and AUC_{0-12} (B) of ALG-097558 in Participants with Normal Renal Function and Severe Renal Impairment

TABLE 3. STATISTICAL ASSESSMENT OF IMPACT OF HEPATIC/RENAL IMPAIRMENT ON PK PARAMETERS

PK Parameter	Population	N	Geometric LS Mean	Ratio* (90% CI)
C_{max} (ng/mL)	Moderate Hepatic Impairment	8	2570	1.05 (0.75, 1.47)
	Normal Hepatic Function	7	2450	
AUC_{0-12} (ng·h/mL)	Moderate Hepatic Impairment	8	11600	1.10 (0.87, 1.39)
	Normal Hepatic Function	7	10600	
C_{max} (ng/mL)	Severe Renal Impairment	6	4510	1.38 (0.92. 2.09)
	Normal Renal Function	6	3270	
AUC_{0-12} (ng·h/mL)	Severe Renal Impairment	6	23800	1.66 (1.03, 2.67)
	Normal Renal Function	6	14300	

*Ratio of PK parameters in participants with hepatic or renal impairment vs. demographically matched healthy subjects

CONCLUSION

- **Moderate hepatic impairment resulted in <2-fold increase in mean total and unbound plasma exposures of both ALG-097558 and the metabolite ALG-097730 compared to demographic-matched participants without hepatic impairment**
- **Severe renal impairment resulted in <2-fold increase in mean plasma exposures of both ALG-097558 and ALG-097730 in participants compared to with severe renal impairment relative to demographic-matched participants without renal impairment**
- **As there was no clinically meaningful impact on the PK, ALG-097558 dose adjustment is not necessary in hepatically (moderate and mild) or renally (mild to severe) impaired individuals**

REFERENCES 1. Wilkes et al. RespiDart 2024

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