RENCOFILSTAT (CRV431) in NASH Patients: The Phase 2a AMBITION Study

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INTRODUCTION

Nonalcoholic Steatohepatitis (NASH): Global prevalence is increasing worldwide with significant morbidity and mortality and no approved pharmacotherapy.

RENCOFILSTAT is a clinical phase drug candidate that inhibits cyclophilin isomerases and attenuates hepatic fibrosis in multiple NASH rodent models.

OBJECTIVES

- To assess the safety, tolerability, and pharmacokinetics (PK) of RENCOFILSTAT in subjects with presumed NASH fibrosis stage 2 or 3 (primary endpoints)
- Exploratory endpoints evaluated NASH biomarkers (transaminases, Enhanced Liver Fibrosis (ELF)-score, Pro-C3, Fibroscan, collagens, matrix metalloproteinases, whole blood transcriptome, and serum lipidome)

MATERIAL & METHODS

Phase 2a single-blind, placebo-controlled trial (NCT04480710) was conducted at 10 research sites (USA) enrolling 47 completing 43 subjects.

Fig 1: AMBITION: A Phase 2a, **M**ulti-center, Single-**B**lind, Placebo-Controlled, Proof of Concept Study to Evaluate the Safety & **T**olerability of CRV431 Dosed **O**nce Daily in **N**ASH Induced F2 & F3 Subjects

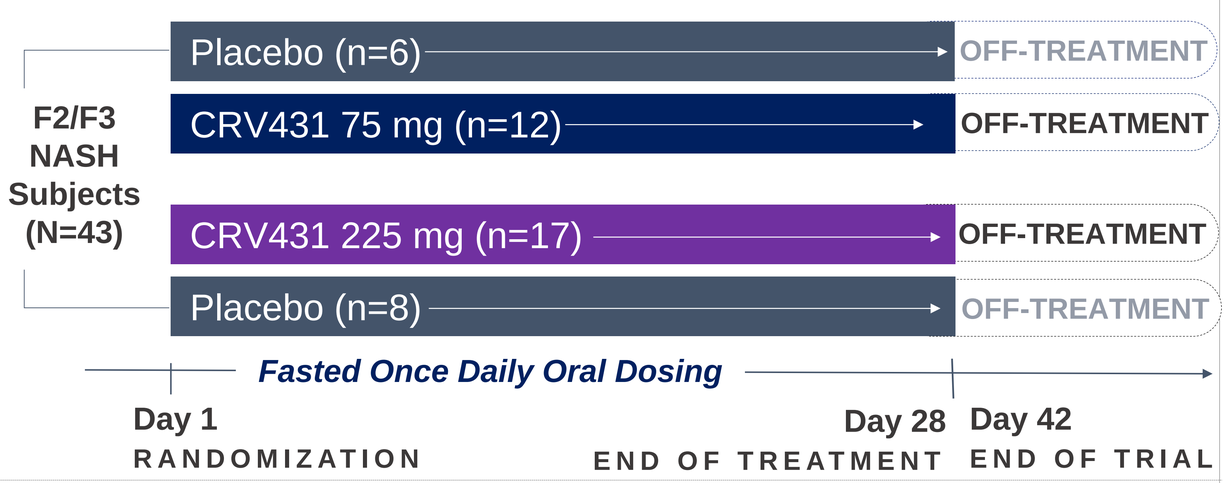


Table 1: Baseline demographics

		CRV431 75 mg (n=12)	CRV431 225 mg (n=17)[a]	Pooled Placebo (n=14)
Age (years)	Mean (SD)	61.9 (8.0)	54.0 (13.3)	61.1 (12.0)
Gender	Male n (%)	7 (58.3)	7 (41.2)	9 (64.3)
Race	White n (%)	11 (91.7)	17 (100)	13 (92.9)
	Hispanic n (%)	1 (8.3)	1 (7.1)	2 (4.7)
BMI (kg/m^2)	Mean (SD)	35.0 (8.0)	37.7 (6.4)	38.9 (8.8)
Pro-C3 (ng/mL)	Mean (SD)	23.8 (8.2)	23.6 (20.0)	22.1 (8.1)
ALT (IU/mL)	Mean (SD)	60.5 (39.1)	36.1 (15.7)	60.8 (33.0)

[a]1 subject with active COVID.

PRIMARY ENDPOINTS

Table 2: Safety: Adverse events related to study drug

- No deaths or SAEs were reported
- Mild AEs include constipation at 75 and 225 mg
- There were 2 patients with mild diarrhea
- 225 mg: 1 report each of fatigue, lips tingling, increased weight, headache, diarrhea and 2 reports of constipation

Figure 2A: RENCOFILSTAT Whole Blood Concentration in NASH and Healthy Subjects (Mean ± 95% CI) 75 mg QD x 28 Days

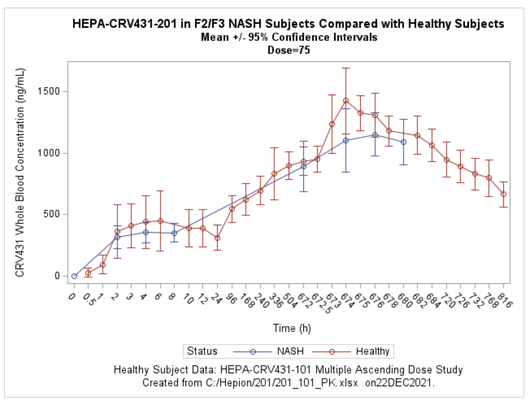
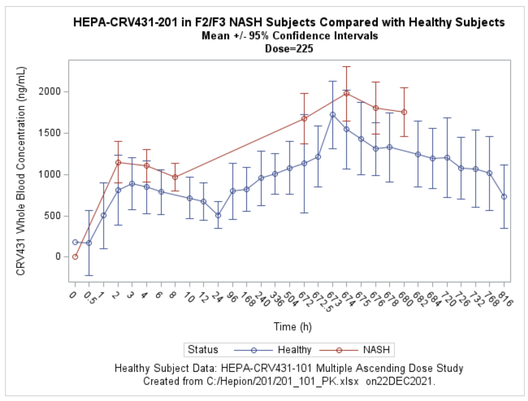
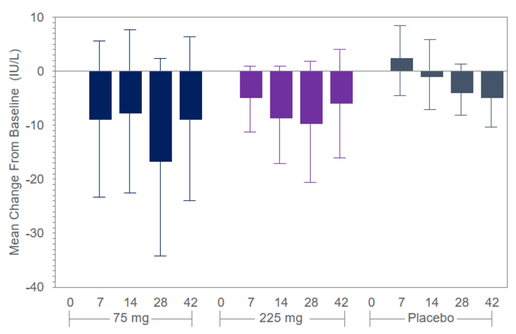


Figure 2B: RENCOFILSTAT Whole Blood Concentration in NASH and Healthy Subjects (Mean ± 95% CI) 225 mg QD x 28 Days



EFFICACY ENDPOINTS: ALT & PRO-C3 PKPD

Figure 3A: Change in ALT Baseline (ng/mL)



PK - PD

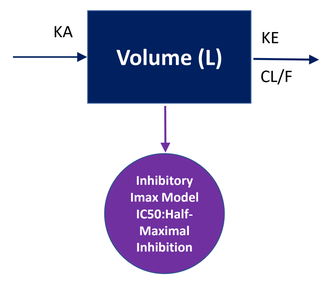


Figure 3C: Predicted vs Observed ALT

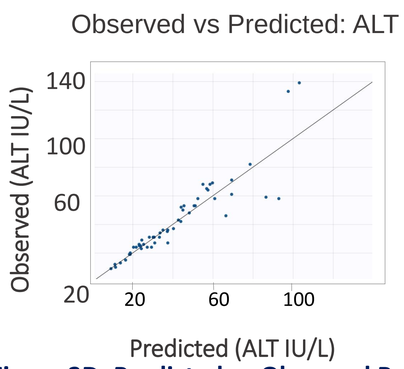
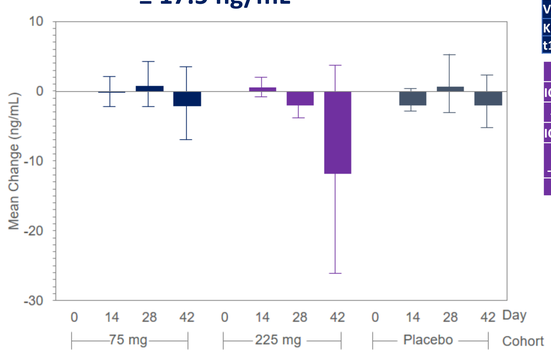


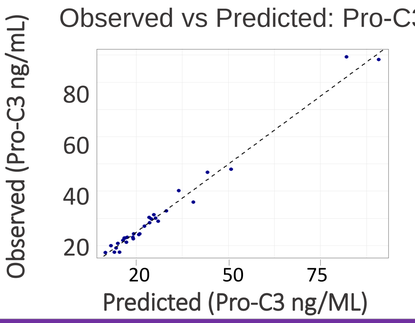
Figure 3B: Change in Pro-C3 from Baseline ≥ 17.5 ng/mL



PK	Estimate*	95% CI**
KA (h-1)	0.82	(0.650 – 0.990)
CL/F (L/h)	4.4	(3.708 - 5.10)
VC/F (L)	203	(180.720 - 225.572)
KE (h-1)	0.02	(0.016 - 0.028)
t1/2KE	32.0	(24.6 - 42.2)

PD	Estimate*	SE	RSE (%)
IC50 ALT	257.98	70.13	27.2
-ALT Baseline	↑		
IC50 – ProC3	918.86	84.28	9.17
-Pro-C3 Baseline	↑		

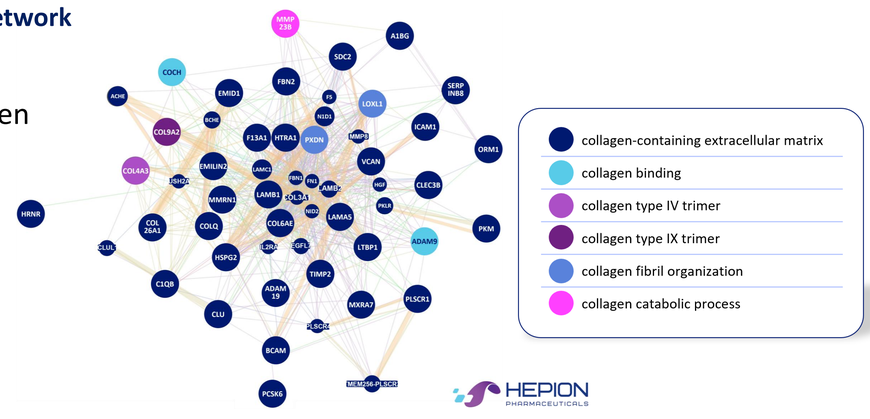
Figure 3D: Predicted vs Observed Pro-C3



EFFICACY ENDPOINTS: Collagen Regulatory Network

Figure 4: Collagen Gene Regulatory Network

- Confirms pre-clinical studies demonstrating decreased collagen formation.
- Suggests anti-inflammatory and collagen catabolic effects.
- Associated with concentrations > 800 ng/mL.



CONCLUSIONS

- RENCOFILSTAT dosed for 28 days at 75 mg or 225 mg was safe and well tolerated
- PK of RENCOFILSTAT in these NASH subjects was similar to healthy subjects
- ALT decreased in 50%, 67%, and 87% of the subjects in the placebo, 75 mg, and 225 mg cohorts, respectively
- In patients with a Pro-C3 Baseline ≥ 17.5 ng/mL ProC3 decreases demonstrated a dose response.
- PK-PD modeling of RENCOFILSTAT concentration accurately predicts ALT and Pro-C3 with a higher IC50 for Pro-C3 than ALT
- Transcriptomics and artificial intelligence (AI) identified a collagen gene regulatory network

CONTACT INFORMATION

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