HEPATIC FUNCTIONAL IMPROVEMENT DETECTED BY HEPQUANT DUO WITHIN 120 DAYS OF TREATMENT WITH RENCOFILSTAT (RCF) IN MASH SUBJECTS WITH ≥ F3 FIBROSIS

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Background

The progression of hepatic fibrosis in MASH has been linked to increased mortality and morbidity. Rencofilstat (RCF), a non-immunosuppressive cyclophilin inhibitor, has previously been found to reduce levels of serum alanine aminotransferase, a marker of liver dysfunction, and of collagen biomarkers associated with fibrosis in MASH subjects[1].

In this Phase 2 study, subjects with advanced fibrosis (F3) were identified using AGILE 3+ score ≥0.53, and treated with 75, 150, or 225 mg RCF for 120 days (Figure 1).

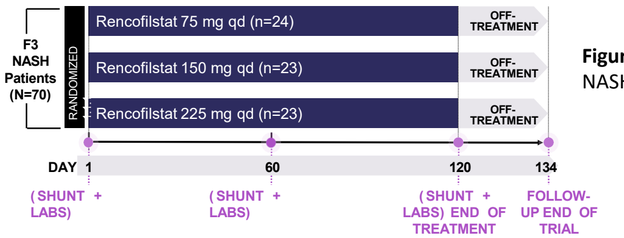

Figure 1. ALTITUDE-NASH trial design.

Liver function and physiology were measured using HepQuant SHUNT, which quantifies effective hepatic perfusion based on the flow-dependent hepatic clearance of cholate from systemic and portal circulations. The test assesses hepatocyte function (cholate uptake), hepatic inflows (portal and systemic clearance) and portal-systemic shunting (SHUNT%). In the SHUNT test, 13C-cholate is injected intravenously and d4-cholate is administered orally, and blood samples obtained over 90 minutes. Liver-specific cholate clearances adjusted for body weight (hepatic filtration rates [HFRs]) are determined from serum concentrations of labeled cholates, and the Disease Severity Index (DSI), portal-systemic shunting (SHUNT%), and hepatic reserve (HR) are calculated from HFRs. DSI ranges from 0 (no disease) to 50 (terminal illness) and correlates with stage of fibrosis, presence of varices, and risk for future clinical outcomes. RISK-ACE relates DSI to annual risk for a clinical event based on long-term follow-up of patients with chronic hepatitis C who had either advanced fibrosis or compensated cirrhosis. In previous research, HepQuant SHUNT test results have been found to predict transition from F3 to compensated cirrhosis, portal hypertension, varices, and adverse clinical outcomes[2,3,4].

Baseline Characteristics

	75 mg (n=24)	150 mg (n=23)	225 mg (n=23)
AST (U/L)	45.0 ± 63.2	24.2 ± 7.8	31.9 ± 21.3
ALT (U/L)	49.6 ± 54.3	31.9 ± 11.7	48.2 ± 42.0
ELF	9.90 ± 1.13	9.64 ± 1.00	9.47 ± 0.51
FibroScan LSM (kPa)	16.8 ± 8.3	13.9 ± 4.8	14.5 ± 8.5
Pro-C3 (ng/mL)	46.3 ± 28.6	36.1 ± 15.6	32.9 ± 6.7
FIB-4	1.65 ± 1.12	1.13 ± 0.53	1.48 ± 0.72

LSMean ± SD

Table 1. Baseline measurements of subjects in the ALTITUDE-NASH trial.

Results

HepQuant Results

HepQuant parameters were assessed at baseline and after 60 and 120 days of treatment. An analysis of HepQuant Duo, the oral component of the HepQuant test, found significant reductions in DSI, SHUNT%, and RISK-ACE in subjects treated with 225 mg RCF, with increases in hepatic reserve, portal HFR, and systemic HFR (Table 2). Decrease of ≥2 DSI units occurred in 10/18 subjects (55.6%) in the 225 mg treatment group after 120 days.

HepQuant DuO Results in the 225 mg/day Rencofilstat Arm

Parameter	Baseline, N=23 Mean(SD)	60 Days, N=21 Mean(SD)	120 Days, N=18 Mean(SD)
DSI	16.44 (3.3)	14.98 (4.1)**	14.79 (3.4)**
SHUNT (%)	24.98(4.9)	22.52 (5.3)**	23.15 (4.6)*
Hepatic Reserve (%)	87.86 (7.5)	90.77 (8.5)**	91.60 (7.5)**
Portal HFR (mL/min/kg)	16.52 (5.5)	20.44 (11.8)*	18.83 (5.2)*
Systemic HFR (mL/min/kg)	3.91 (0.6)	4.09 (0.7)**	4.17 (0.6)**
RISK ACE	2.41	2.07****	1.92****

Change from baseline by paired t-test: *p<0.10, **p<0.05, ***p<0.01, ****p<0.001.
DSI: Disease Severity Index (0-50); HFR: Hepatic Filtration Rate; RISK ACE: Risk of clinical events per person-year

Table 2. Functional hepatic improvement in the 225 mg/day RCF treatment group as assessed by HepQuant DuO. HFRs increased and DSI, SHUNT%, and RISK ACE decreased.

Safety Assessments

Rencofilstat was safe and well tolerated up to 120 days of treatment:

- No subjects discontinued due to TEAEs related to treatment.
- Out of 137 total TEAEs, 97.8%) were Grade 1 or 2. Of the Grade 3 TEAEs, only 1 (blood bilirubin increased) was considered possibly related to treatment.
- There were no treatment-related SAEs.
- The most common TEAEs were nausea, diarrhea, and anemia, which occurred in ≤10% subjects.
- There was no dose relationship to TEAE.

Biomarkers of Fibrosis and Liver Function

Liver fibrosis and function biomarkers were assessed at baseline (Table 1) and after 60 and 120 days treatment. Similar to the HepQuant parameters, differences were observed in the 225 mg RCF treatment group at 120 days (Table 3).

Stratification of the data set by a Pro-C3 threshold of 37.5 ng/mL was selected based on a literature search that demonstrated greater drug effects when Pro-C3 was elevated above 17.5 ng/mL (original ELISA units), which corresponds to 37.5 ng/mL in the assay used in this trial[5].

Biomarkers of Fibrosis and Liver Function in the 225 mg/day Rencofilstat Arm (Day 120)

	225 mg RCF n=21	225 mg RCF (with Baseline Pro-C3 ≥ 37.5 ng/mL); (n=6)
	% Change from Baseline	
AST (U/L)	4.68 ± 31.92*	-11.34 ± 38.54*
ALT (U/L)	-21.63 ± 32.8*	-37.78± 31.42*
ELF	-2.51 ± 6.85*	-5.31 ± 7.02*
Fibroscan LSM (kPa)	-54.97 ± 25.83*	-60.20 ± 9.37*
Pro-C3 (ng/mL)	-9.58 ± 31.56*	-16.23 ± 22.59*
Fib-4	17.90 ± 41.91	-3.5 ± 47.6

*Different from Baseline, Friedman ANOVA (data non-normally distributed).

Table 3. Change from baseline in liver fibrosis and function biomarkers are shown for the 225 mg RCF treatment group after 120 days treatment. In addition, subjects with elevated Pro-C3 (≥37.5) at baseline are shown.

Discussion and Conclusions

The ALTITUDE-NASH trial evaluated ≥F3 MASH subjects treated with RCF for 120 days. Efficacy measures showed significant reductions of HepQuant DSI score, SHUNT%, and RISK ACE in subjects treated with 225 mg RCF. RCF was safe and well-tolerated, with most subjects completing the trial and minimal treatment-related events. The main conclusions are:

- Use of AGILE 3+ score identifies a population of ≥F3 MASH subjects at high risk of clinical complications.
- HepQuant noninvasive measurements enabled an evaluation of hepatic function through examination of portal and systemic filtration rates and calculation of DSI.
- Rencofilstat showed efficacy in improving HepQuant parameters in the 225 mg dosage group after 60 and 120 days treatment.
- Rencofilstat was safe and well-tolerated, with minimal treatment-related adverse events.

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Disclosures

SAH is a paid consultant of Hepion Pharmaceuticals, Inc.
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