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

Rencofilstat (RCF), a non-immunosuppressive cyclophilin inhibitor, has been found to reduce levels of collagen biomarkers associated with fibrosis (ProC3) and serum transaminases (ALT and AST), markers of liver damage.[1] The effects of RCF on hepatic function and portal-systemic shunting were examined in ≥F3 NASH subjects using the HepQuant DuO test. Other objectives of the study were to assess safety, tolerability, transcriptomics and pharmacokinetics of RCF.

Advanced fibrosis (F3) was identified using an AGILE 3+ score ≥0.53. Subjects were randomized to RCF at 75, 150, or 225 mg RCF for 120 days.

Liver function and physiology were measured using HepQuant DuO, which quantifies effective hepatic perfusion based on the flow-dependent hepatic clearance of d4-cholate from systemic and portal circulations. In the DuO test d4-cholate is administered orally, and blood samples obtained at 20 and 60 minutes. The test determines, hepatic filtration rate (HFR), from which Disease Severity Index (DSI), portal-systemic shunting (SHUNT%), and hepatic reserve (HR) are calculated. 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[2,3,4]. RNA sequencing was for exploratory purposes. Population Pharmacokinetics were run using NonMem v7.5. Differential gene expression was run in edgeR (v3.36.0). Only protein encoding genes were analyzed for mechanism of action modeling.

Baseline Characteristics

Biomarkers of Fibrosis and Liver Function

Liver fibrosis biomarkers were assessed at baseline (Table 1).

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

	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

Results

HepQuant Duo liver function parameters are depicted in Table 2 at baseline, Day 60 and Day 120 for the 225 mg dose only. Efficacy was observed in the 75 mg and 150 mg dosing arms as a function of RCF concentration and is the subject of a more detailed PKPD analysis (not shown).

Fibrosis biomarkers are shown as percentage and absolute change from baseline at Day 120 in the 225 mg dose in 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].

Results

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.

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. No multiplicity adjustment

DSI: Disease Severity Index (0-50); HFR: Hepatic Filtration Rate; RISK ACE: Risk of clinical events per person-year

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.

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: Mean (95%CI)		
AST %	4.68(-10.26,19.62)	-11.34(-51.75,29.08)*
ALT %	-21.63(-35.56,-6.70)*	-37.78(-70.75,-4.81)*
ELF %	-2.51(-5.62,0.61)	-5.31(-12.68,2.05)*
Fibroscan LSM %	-28.84(-44.25,-13.42)*	-37.35(-52.34,-22.36)*
Pro-C3 %	-9.58 ± 31.56*	-16.33(-39.94,7.47)*
Fib-4	17.90 ± 41.91	-3.5(-53.48,46.48)
Absolute Change From Baseline: Mean(95%CI)		
AST (IU/L)	-2.89(-11.19,5.51)	-11.83(-41.41,17.74)
ALT (IU/L)	-12.10 (-23.06,-1.13)*	-27.67(-67.22,11.89)
ELF	-0.25(-0.55,0.06)	-0.50(-1.38,0.38)
Fibroscan LSM (kPa)	-6.02 (-10.48, -1.56)*	-6.03(-9.99,-20.8)*
ProC3 (ng/mL)	-4.98(-10.82,0.86)	-8.65(-22.16,4.86)
Fib4	-0.21 ± 2.07	-1.50(-5.41,2.41)

*Different from Baseline, LSMeans with ProcGLM Ranks

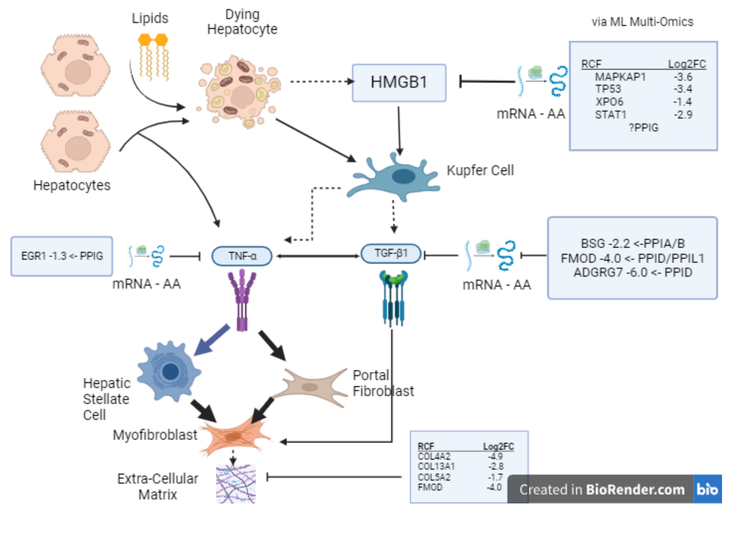
PK

Table 4. Population Pharmacokinetics

Parameter	Estimate	SE	RSE	95%CI
exponential error	0.459	0.0584	12.7%	0.345 - 0.573
KA (h-1)	0.295	0.0975	33.1%	0.104 - 0.486
CL/F (L/h)	5.48	1.19	21.7%	3.148 - 7.812
VC/F (L)	91.4	23.3	25.5%	45.732 - 137.068

Transcriptomics MOA

Figure 1. Transcriptomics & RCF MOA in MASH F3 Subjects



Safety

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.

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.
- Pharmacokinetics support once daily dosing in MASH F3 Subjects.
- Transcriptomic Analysis of protein-encoding genes supports the proposed mechanism of action that cyclophilin inhibition works at multiple sites to regulate inflammation and collagen regulation.
- Rencofilstat was safe and well-tolerated, with minimal treatment-related adverse events.

References

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