USE OF AGILE 3+ AS A SCREENING TOOL SUCCESSFULLY TARGETS F3 MASH SUBJECTS WITH IMPAIRED HEPATIC FUNCTION AND PORTAL-SYSTEMIC SHUNTING EVALUATED BY HEPQUANT SHUNT TEST: LESSONS LEARNED FROM THE HEPION ALTITUDE-NASH TRIAL

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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 studied in Phase 1 trials in healthy volunteers and a Phase 2 trial in MASH subjects. In a previous Phase 2 trial, 225 mg RCF taken daily (QD) for 28 days reduced levels of serum alanine aminotransferase, a marker of liver dysfunction, and of collagen biomarkers associated with fibrosis[1].

This Phase 2 study examined the effects of RCF on MASH subjects with F3 fibrosis, who were selected for inclusion based on AGILE 3+ score ≥0.53 and absence of cirrhosis. AGILE 3+ combines aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, platelet count, diabetes status, sex, age, and liver stiffness measurement to determine liver fibrosis, and has been shown to accurately assess disease severity and prognosis in MASH subjects[2].

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), 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[3,4,5].

Methodology

Seventy F3 MASH subjects were enrolled based on AGILE 3+ score ≥0.53 and absence of cirrhosis, and randomized to receive 75, 150, or 225 mg oral RCF daily for 120 days. HepQuant was assessed at Baseline, Day 60, and Day 120 along with measures of liver health and fibrosis including AST, ALT, ELF, Fibroscan, Pro-C3, and FIB-4 (Table 1). Baseline characteristics and validity of measures are assessed here.

Results of the trial can be viewed at Paper #5032-C on Monday 11/13.

Baseline Characteristics

Baseline characteristics were consistent with an F3 MASH subject population (Table 1).

	75 mg RCF (n=24)	150 mg RCF (n=23)	225 mg RCF (n=23)
Age (year)	61.5 ± 9.6	57.4 ± 9.9	61.0 ± 8.9
Sex (% female)	37.5	60.9	43.5
Diabetes (%)	70.8	73.9	69.6
BMI	36.6 ± 7.4	39.9 ± 6.2	37.6 ± 8.1
AGILE 3+	0.75 ± 0.18	0.73 ± 0.13	0.70 ± 0.14
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 characteristics of subjects in the ALTITUDE-NASH trial.

Consistent with an F3 population, about half of subjects had significant hepatic functional impairment as determined by HepQuant DSI score >18.3, of which a quarter had elevated portal-systemic shunting (SHUNT% >27%) (Figure 1).

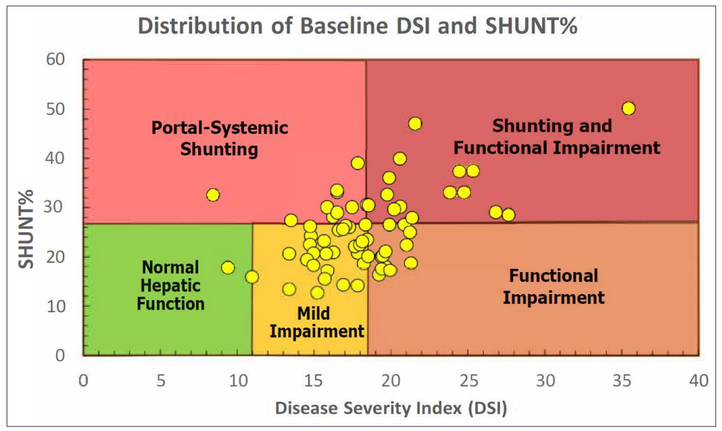

Figure 1. Baseline HepQuant results. DSI score (0-50) and SHUNT% correlated and were consistent with an F3 MASH population with mild to moderate hepatic impairment.

Baseline Characteristics

HepQuant and other hepatic parameters were evaluated based on baseline Pro-C3 score < or ≥37.5. The 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]. There was an association between Pro-C3 score and higher ALT/AST values (Figure 2).

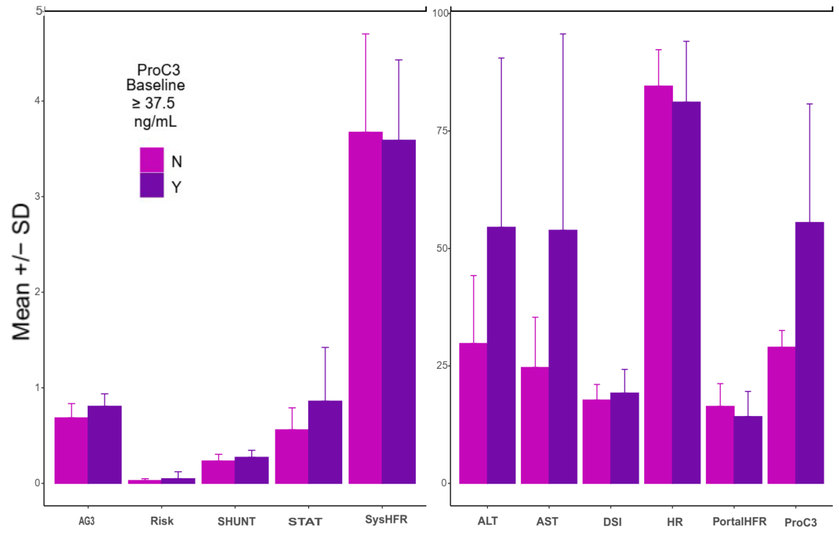

Figure 2. Hepatic parameters separated by baseline Pro-C3 <37.5 (magenta) or ≥37.5 (purple). The strongest association was with alanine aminotransferase (ALT) and aspartate transaminase (AST). AG3: Agile 3+; RISK: RISK ACE; STAT: d4-cholate concentration at 60 minutes; HR: hepatic reserve.

Discussion and Conclusions

- Agile 3+ (≥0.53) performed well to select ≥F3 subjects.
- HepQuant SHUNT assessments showed a population with mild-to-moderate functional impairment.
- Pro-C3 baseline ≥37.5 ng/mL revealed subjects with greater disease activity as demonstrated by higher ALT and AST levels.
- Hepatic function as measured by HepQuant was not associated with baseline Pro-C3 ≥37.5.
- Pro-C3 baseline may provide a valuable addition to Agile 3+ for detecting disease activity vs chronicity.
- Function and activity reveal heterogeneity critical for clinical treatment and clinical trial inclusion.

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Disclosures

SAH is a paid consultant of Hepion Pharmaceuticals, Inc.
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