LBP-18

Effect of Obeticholic Acid on Liver Function in Patients With Fibrosis due to NASH

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Introduction

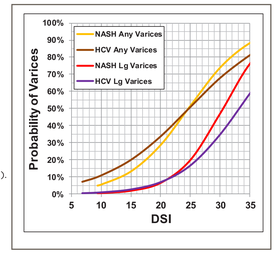
- Nonalcoholic steatohepatitis (NASH) is a chronic liver disease associated with increased metabolic comorbidities and can progress to cirrhosis, hepatocellular carcinoma and liver-related death[1]
- Obeticholic acid (OCA), a potent, selective farnesoid X receptor (FXR) agonist, improved advanced fibrosis due to NASH in patients in the pivotal Phase 3 REGENERATE study[2]
- In this study (747-117), the HepQuant® SHUNT test (HepQuant)* was used to evaluate the effect of OCA on liver function improvements in patients with fibrosis due to NASH
- HepQuant measures the clearance of labeled cholate from systemic and portal circulations as a marker of liver function[3]
  - It is used to derive the Disease Severity Index (DSI), a global score of liver function that has been shown to correlate with clinical outcomes

The HepQuant SHUNT Liver Diagnostic Kit is not FDA-approved.
The HepQuant SHUNT Liver Diagnostic Kit was evaluated in 747-117 study under IDE G170034/S003.

LINK OF HEPQUANT'S DSI TO PERCENT LIKELIHOOD OF ENDOSCOPIC FINDING OF VARICES IN PATIENTS WITH NASH OR HCV[4]

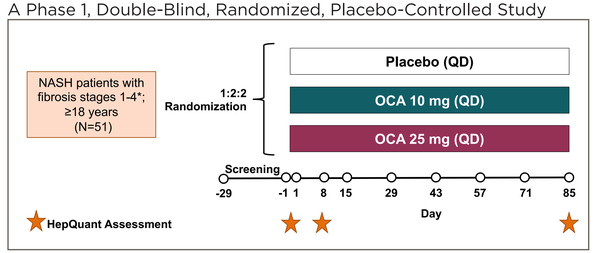
- DSI score has been correlated with varices in patients with NASH and Hepatitis C (HCV)
- A 2-point reduction in DSI is proposed as clinically meaningful
  - Based on reducing likelihood of any varices from ~30% to 20% for patients with a baseline DSI of 20

EGDs and DSI N=248; NASH N=31 (Any Varices n=14, Lg Varices n=9); HCV N=217 (Any Varices n=74, Lg Varices n=22).



STUDY DESIGN

A Phase 1, Double-Blind, Randomized, Placebo-Controlled Study



*Defined as histologic evidence of NASH with fibrosis stage 1 to 4 based on a liver biopsy obtained ≤24 months before Day -1 per the NASH CRN scoring criteria.

EXPLORATORY ANALYSIS OBJECTIVES

Assess the change in liver function after 85 days of OCA treatment (10 mg or 25 mg) relative to placebo

- Characterize the baseline liver function of patients with NASH and varying degrees of fibrosis (F1 to F4)
- Compare the improvement in liver function, using DSI as a surrogate, in patients with NASH from study 747-117 with the histological improvement in fibrosis stage* observed in the REGENERATE study

*Per the NASH CRN scoring criteria.

Methods

- Liver function was characterized using the HepQuant SHUNT minimally-invasive Liver Diagnostic Kit
- Labeled cholate was administered intravenously and orally on Day -1 (baseline), Day 8, and Day 85 for HepQuant assessment
  - Day 8 assessments were included to assess the potential for drug-drug interactions (DDI) between cholate and OCA
    - No statistically significant effect was observed
- Responder analysis was based on a 2-point or greater decrease in DSI from Day 1 to Day 85

Results

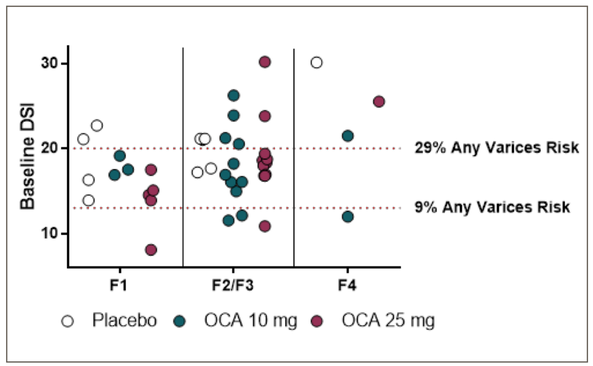
Baseline characteristics (N=43)

Of the 51 randomized patients, 45 patients had a DSI assessment at baseline and 43 patients had both a baseline and Day 85 DSI assessment

Parameters	Placebo (n=10)	OCA 10 mg (n=16)	OCA 25 mg (n=17)
Age, years	57 (12)	57 (14)	56 (9)
Female, n (%)	7 (70)	16 (100)	10 (60)
White, n (%)	10 (100)	14 (88)	17 (100)
BMI, kg/m²	34 (5)	36 (4)	34 (4)
Diabetes at Baseline, n (%)	5 (50)	14 (88)	10 (59)
Liver Fibrosis Stage*, n (%)			
F1	4 (40)	3 (19)	5 (29)
F2	0	4 (25)	3 (18)
F3	5 (50)	7 (44)	8 (47)
F4	1 (10)	2 (13)	1 (6)
NAS	5 (1)	5 (1)	5 (1)
ALT, U/L	63 (38)	48 (23)	41 (20)
AST, U/L	53 (30)	41 (19)	32 (15)
ALP, U/L	115 (35)	90 (30)	93 (34)
Total Bilirubin, µmol/L	13 (7)	9 (4)	9 (3)
INR	1 (0.1)	1 (0.1)	1 (0.1)
Platelets, x10³/L	201 (73)	215 (62)	219 (56)

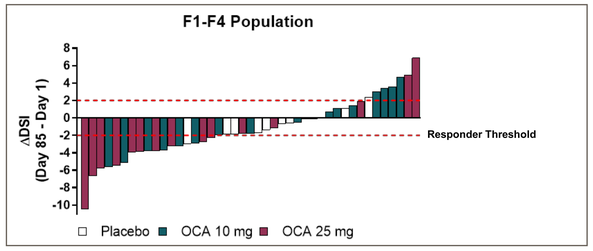
*Per the NASH CRN scoring criteria.
Data are Mean (SD), unless otherwise noted.

BASELINE DSI ASSESSMENT



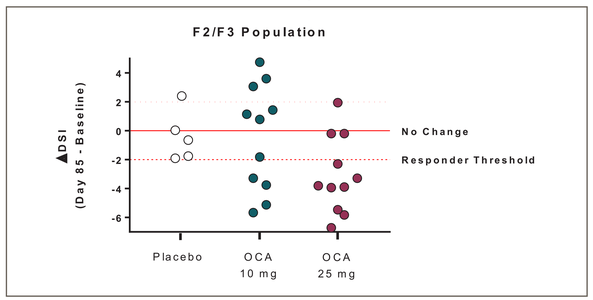
- Baseline DSI assessment:
  - Tended to increase with increasing fibrosis stage
    - DSI scores over 20, indicative of an increased risk for varices, especially large varices, were more common with advanced fibrosis stage
  - Varied within and across fibrosis stages, indicating a wide range of hepatic dysfunction across the patient population

CHANGE IN DSI AT DAY 85 IN ALL PATIENTS (F1-F4)



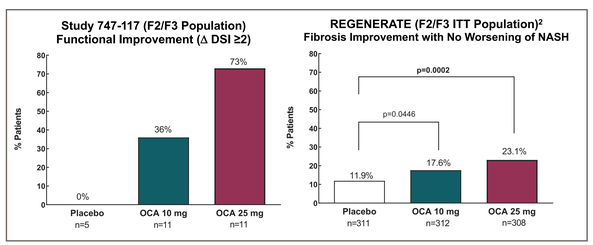
- OCA dose-dependently improved DSI compared to placebo over 85 days of treatment
- 17 out of 18 responders were treated with OCA
  - OCA 25 mg had a greater impact on DSI than OCA 10 mg
- Majority of placebo patients remained within the 2-point range
- In patients with a greater than 2-point increase in DSI, no hepatic safety events or adverse trends in liver enzymes or pruritus were observed

CHANGE IN DSI AT DAY 85 IN F2/F3 PATIENTS



- OCA treatment for 85 days was associated with a dose-dependent reduction in DSI in patients with F2/F3 fibrosis due to NASH
  - The majority of OCA 25 mg patients had clinically significant change in DSI

RESPONDERS



- A dose-dependent and clinically meaningful reduction in DSI was observed for OCA 10 mg and OCA 25 mg
  - DSI response was greater with OCA 25 mg
- Dose-dependent response in DSI was consistent with the dose-dependent improvement in fibrosis observed in REGENERATE

SAFETY

- No serious adverse events were reported
- Pruritus was the most common adverse event [placebo 4/10 (40%), OCA 10 mg 3/16 (19%), OCA 25 mg 4/17 (24%)]
  - Most events were mild to moderate in severity
  - No patients discontinued due to pruritus
- There were no discontinuations due to treatment-emergent adverse events
- Consistent with findings from previous NASH studies, a modest increase in LDL cholesterol was observed in the OCA groups

Conclusions

- The patients in this study were generally representative of the population in REGENERATE and represented a broad range of hepatic function
- This is the first demonstration of OCA eliciting a dose-dependent clinically significant improvement in liver function in patients with NASH*
- Early improvement in DSI, measured by a 2-point reduction, over approximately 3 months, may have potential as a functional biomarker to predict subsequent histological or clinical improvement in patients with advanced fibrosis due to NASH
  - Based on DSI in chronic HCV, we hypothesize that the improvements in DSI with NASH patients could translate into reduced risk for clinical outcomes
- The dose-dependent improvement in liver function in F2/F3 patients observed in this study is consistent with the dose-dependent improvement in fibrosis observed in REGENERATE
  - This further supports the efficacy of OCA treatment in patients with advanced fibrosis due to NASH

*The 2-point decrease in DSI as an indicator of positive treatment effect and the analysis of the results of the HepQuant test in 747-117 were defined and executed prior to any knowledge of the results from REGENERATE.

References

1. Vernon G, et al. *Aliment Pharmacol Ther*. 2011;34(3):274-285.
2. Younossi Z, et al. Presented at EASL 2019, Vienna, Austria (Oral GS-06).
3. Shrestha R, et al. *Liver Transpl Surg*. 1997;3(2):166-73.
4. Helmke S, et al. Presented at NASH Biomarkers. 2017 (Poster 15).

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Disclosure

NA – Nothing to disclose; GTE – Employment: HepQuant LLC, Patent held/filed: Univ Colorado, ***SH*** – Employment and Patent held/filed: HepQuant LLC; ***JC/CL/MS/JEE*** – Employment and stock shareholder: Intercept Pharmaceuticals.

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General hepatology
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