Poster # LBP-036

Final results from the phase 3 REGENERATE trial evaluating the effects of obeticholic acid in patients with pre-cirrhotic fibrosis due to metabolic dysfunction–associated steatohepatitis

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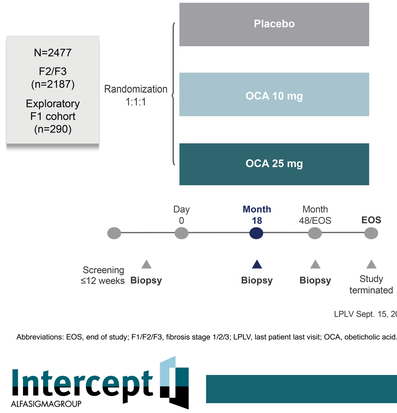
Introduction

- Fibrosis is the strongest predictor of clinical outcomes in metabolic dysfunction–associated steatohepatitis (MASH), such as cirrhosis[1,2]
- Obeticholic acid (OCA) is a first-in-class farnesoid X receptor agonist that has been shown to reverse or reduce fibrosis progression in preclinical and clinical studies[3]
- The phase 3 REGENERATE study (NCT02548351) was designed to evaluate the impact of OCA on progression to clinical outcomes over a minimum of 4 years of follow-up in patients with MASH
  - A consensus re-analysis of the 18-month interim results demonstrated that the proportion of patients treated with OCA 25 mg who achieved the primary endpoint of ≥1 stage histologic improvement in fibrosis with no worsening of MASH was significantly higher than that of patients treated with placebo (22.4% vs 9.6%, *P*<0.0001)[4]
  - REGENERATE was prematurely terminated in September 2023 after OCA did not receive marketing approval following the consensus re-analysis
- Here, we present the final end-of-study results from REGENERATE

Methods

- REGENERATE was a multicenter, randomized, double-blind, placebo-controlled study
- Patients were randomized 1:1:1 to placebo, OCA 10 mg, or OCA 25 mg (**Figure 1**)
- Key inclusion criteria were adults age ≥18 years, with biopsy-confirmed MASH with fibrosis stage F2 or F3 and metabolic dysfunction-associated steatotic liver disease activity score ≥4
- Key exclusion criteria included alanine aminotransferase or aspartate aminotransferase levels ≥10× upper limit of normal, total bilirubin >1.5 mg/dL, platelet count <10^5/m^3, hemoglobin A1c >9.5%, histologic evidence of cirrhosis, evidence of other chronic liver disease, or significant alcohol consumption
- The primary composite endpoint was time to first occurrence of death (all cause); model for end-stage liver disease score ≥15; liver transplant; hospitalization for variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis; ascites secondary to cirrhosis and requiring medical intervention; or progression to cirrhosis
  - Progression to cirrhosis was defined histologically using MASH Clinical Research Network criteria
- Secondary histologic endpoints included 1) improvement of fibrosis by ≥1 stage with no worsening of MASH or 2) improvement of fibrosis by ≥1 stage with no worsening of MASH or MASH resolution with no worsening of fibrosis stage
- Efficacy was assessed in the intent-to-treat population (N=2187) and safety was assessed in all randomized patients who received ≥1 dose of investigational product (IP; N=2477)
- All outcomes, including progression to cirrhosis, were adjudicated by an independent expert committee
- Safety endpoints included treatment-emergent adverse events (TEAEs); adjudicated cardiovascular, hepatic, and acute kidney injury events; vital signs, electrocardiograms, and clinical laboratory results

Figure 1. REGENERATE study design



LPLV Sept. 15, 2023

Abbreviations: EOS, end of study; F1/F2/F3, fibrosis stage 1/2/3; LPLV, last patient last visit; OCA, obeticholic acid.

Results

Baseline characteristics

- Baseline demographics and clinical characteristics were balanced across treatment groups (**Table 1**)

Table 1. Baseline demographics and clinical characteristics of patients in the REGENERATE study

	Placebo (n=825)	OCA 10 mg (n=825)	OCA 25 mg (n=827)
Age, mean ± SD, y	54.4±11.2	55.3±10.8	55.3±11.7
Female, n (%)	478 (57.9)	475 (57.6)	494 (59.7)
Race, n (%)[a]			
American Indian or Alaska Native	6 (0.7)	5 (0.6)	8 (1.0)
Asian	29 (3.5)	47 (5.7)	43 (5.2)
Black or African American	12 (1.5)	14 (1.7)	20 (2.4)
Native Hawaiian or Other Pacific Islander	2 (0.2)	4 (0.5)	4 (0.5)
White	685 (83.0)	679 (82.3)	674 (81.5)
Other	7 (0.8)	4 (0.5)	3 (0.4)
BMI, mean ± SD, kg/m²	34.1±5.5	33.7±5.6	33.7±5.5
ALT, mean (SD), U/L	77.1 (51.7)	71.4 (46.3)	72.5 (52.5)
AST, mean (SD), U/L	56.2 (36.6)	53.3 (32.1)	52.8 (32.8)
TB, mean (SD) , mg/dL	0.66 (0.32)	0.66 (0.30)	0.68 (0.35)
LDL ≥100 mg/dL, n (%)	496 (60.9)	489 (60.2)	511 (62.5)
Diabetes, n (%)	470 (57.0)	476 (57.7)	479 (57.9)
Medical history, n (%)			
Cholelithiasis	161 (19.5)	149 (18.1)	160 (19.3)
Hypertension	556 (67.4)	553 (67.0)	538 (65.1)
Cardiac disorders	119 (14.4)	130 (15.8)	125 (15.1)
Renal and urinary disorders	189 (22.9)	211 (25.6)	187 (22.6)
Concomitant medication use, n (%)			
Bile acid sequestrants	18 (2.2)	13 (1.6)	22 (2.7)
Statins	377 (45.7)	359 (43.5)	379 (45.8)
GLP-1 agonists	74 (9.0)	83 (10.1)	79 (9.6)
Thiazolidinedione	14 (1.7)	13 (1.6)	15 (1.8)
Vitamin E	86 (10.4)	71 (8.6)	81 (9.8)

[a]Percentages do not add to 100 because some patients were missing data.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GLP-1, glucagon-like peptide 1; LDL, low-density lipoprotein; OCA, obeticholic acid; TB, total bilirubin.

Efficacy

- Composite outcome events occurred in 18.8%, 15.8%, and 14.7% of patients treated with placebo, OCA 10 mg, and OCA 25 mg, respectively (**Table 2**)
- Compared with placebo, the hazard ratio was 0.814 for OCA 10 mg and 0.772 for OCA 25 mg, which was driven by fewer OCA-treated patients progressing to cirrhosis (**Table 2**)

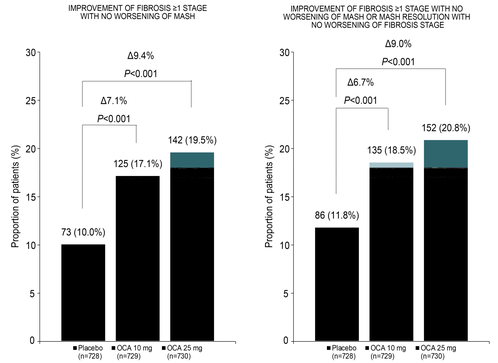
Table 2. Primary efficacy analysis: time to first composite outcome event (ITT population)

	Placebo (n=728)	OCA 10 mg (n=729)	OCA 25 mg (n=730)
Patients with any event,[a] n	137	115	107
Patients with any event, % (95% CI)	18.8 (16.0–21.9)	15.8 (13.2–18.6)	14.7 (12.2–17.4)
Mean rate difference (95% CI)		–3.0 (–6.9 to 0.8)	–4.2 (–8.0 to –0.4)
Stratified log-rank test *P* value vs placebo[b]		0.103	0.044
Stratified hazard ratio vs placebo (95% CI)[c]		0.814 (0.635–1.043)	0.772 (0.600–0.994)
Death, n (%)	9 (1.2)	7 (1.0)	11 (1.5)
Liver transplant, n (%)	0	1 (0.1)	1 (0.1)
MELD score ≥15, n (%)	2 (0.3)	4 (0.5)	2 (0.3)
Hospitalization for complications of hepatic decompensation, n (%)	0	1 (0.1)	2 (0.3)
Ascites secondary to cirrhosis requiring medical intervention, n (%)	0	3 (0.4)	4 (0.5)
Progression to cirrhosis, n (%)	126 (17.3)	99 (13.6)	87 (11.9)

[a]Patients were counted only once by the first event if multiple events occurred. Patients were censored at the last contact date if no event was observed.
[b]Statistical significance for clinical outcomes was set at *P*=0.03 (remaining alpha from month 18 interim analysis). The log-rank test compared each treatment group with placebo stratified by baseline diabetes status and use of thiazolidinediones or vitamin E at baseline.
[c]The hazard ratio (95% CI) was calculated using a Cox regression model with baseline diabetes status and use of thiazolidinediones or vitamin E at baseline included in the model.
Abbreviations: CI, confidence interval; ITT, intent to treat; MELD, model of end-stage liver disease; OCA, obeticholic acid.

- More OCA-treated patients had fibrosis improvement ≥1 stage with no worsening of MASH compared with placebo (*P*<0.001 for both dose groups; **Figure 2**)

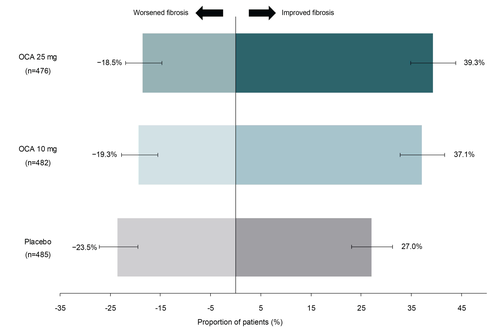
Figure 2. Histology endpoints in patients with MASH treated with placebo, OCA 10 mg, or OCA 25 mg at end of study (ITT population)



Analysis includes the last post-baseline biopsy score regardless of visit or time window.
P values, calculated using the Cochran-Mantel-Haenszel test, are nominal and provided only for descriptive purposes.
Abbreviations: ITT, intent to treat; MASH, metabolic dysfunction–associated steatohepatitis; OCA, obeticholic acid.

- From baseline to end of study, fibrosis improved by ≥1 stage in 27.0%, 37.1%, and 39.3% of patients treated with placebo, OCA 10 mg, and OCA 25 mg, respectively (**Figure 3**). Fibrosis worsened by ≥1 stage in 23.5%, 19.3%, and 18.5% of patients in these treatment groups, respectively

Figure 3. Shift in fibrosis stage from baseline to end of study (ITT population)



Error bars indicate 95% confidence intervals.
Abbreviations: ITT, intent to treat; OCA, obeticholic acid.

Safety

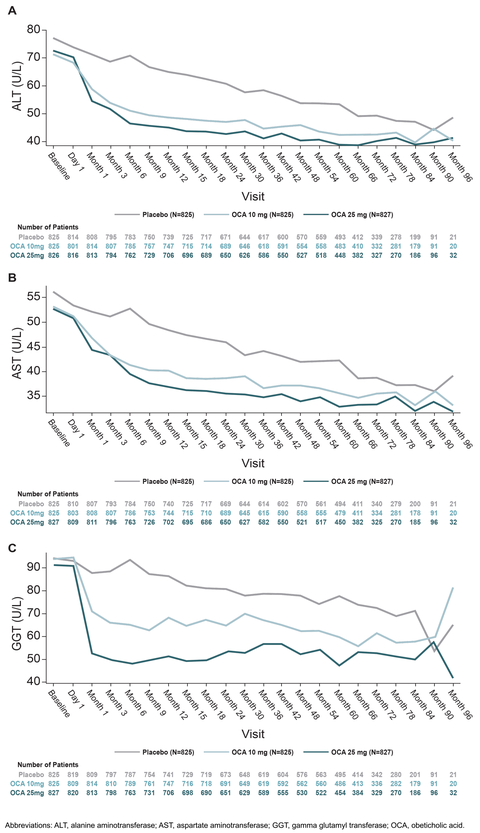
- Patients had a median exposure to IP for >4 years (**Table 3**)
- OCA treatment resulted in dose-dependent reductions in mean serum alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase levels to a greater extent than placebo treatment (**Figure 4**)
- TEAEs, serious TEAEs, and deaths were similar across groups (**Table 3**)
- Consistent with the month 18 analysis,[4] pruritus was the most frequent TEAE leading to IP discontinuation (**Table 3**)
- Serious gallbladder disease and related complications TEAEs occurred more frequently with OCA 25 mg (27/827 [3.3%] patients) than with OCA 10 mg (11/825 [1.3%] patients) or placebo (8/825 [1.0%] patients)

Table 3. Exposure to IP and TEAEs in the safety population (N=2477)

	Placebo (n=825)	OCA 10 mg (n=825)	OCA 25 mg (n=827)
Median patient exposure years	4.6	4.5	4.1
Total patient exposure years	9.4	9.2	8.4
Deaths, n (%)	9 (1.1)	8 (1.0)	11 (1.3)
TEAEs, n (%)	781 (94.7)	798 (96.7)	813 (98.3)
Serious TEAEs, n (%)	216 (26.2)	245 (29.7)	248 (30.0)
TEAEs leading to treatment discontinuation, n (%)	111 (13.5)	118 (14.3)	206 (24.9)
Most frequent TEAE: pruritus, n (%)	207 (25.1)	289 (35.0)	467 (56.5)
Most frequent TEAE leading to IP discontinuation: pruritus, n (%)	8 (1.0)	16 (1.9)	113 (13.7)

Abbreviations: IP, investigational product; OCA, obeticholic acid; TEAE, treatment-emergent adverse event.

Figure 4. Mean serum levels of ALT (**A**), AST (**B**), and GGT (**C**) in patients treated with OCA vs placebo over time



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; OCA, obeticholic acid.

Conclusions

- At end of study, REGENERATE demonstrated a benefit in clinical outcomes, and histologic progression to cirrhosis was reduced in patients receiving OCA 25 mg
- These data confirm the antifibrotic benefit of OCA observed at month 18 and support OCA-related effects on fibrosis
- The safety results add to the largest safety database in MASH, with a median OCA exposure of ~52 months. There were no new safety concerns with >2 years of additional exposure

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