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OBETICHOLIC ACID (OCA) IMPROVES NONINVASIVE MARKERS OF FIBROSIS IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS (NASH): A SECONDARY ANALYSIS OF THE PHASE 3 REGENERATE STUDY

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INTRODUÇÃO

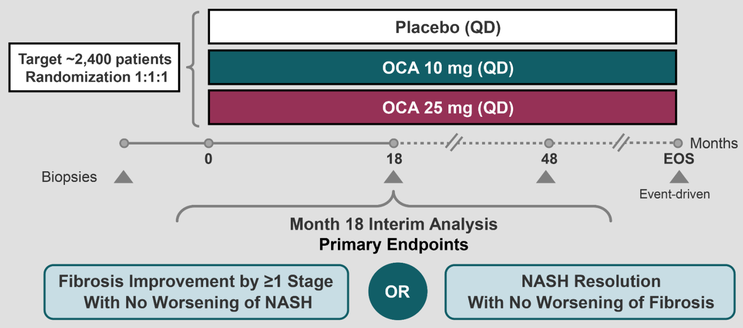
- NASH is a widespread, chronic liver disease that can progress to cirrhosis.[1] There are no approved therapies for NASH at this time
- OCA, a potent and selective farnesoid X receptor (FXR) agonist, improves liver fibrosis and NASH[2,3]
- Treatment with OCA 25 mg for 18 months led to significant improvement in "fibrosis with no worsening of NASH" compared with placebo (p=0.0002)[4] in a prespecified 18-month interim analysis of the REGENERATE phase 3 study
  - The study is ongoing through clinical outcomes to characterize OCA's clinical benefit
- Noninvasive tests (NITs) are predictive of histologic changes and liver-related outcomes in NASH[5]
- Liver biopsy is widely used in clinical trials, but is less commonly used in clinical practice; fibrosis stages evaluated by biopsy span a broad range of histopathologic injury and may underestimate meaningful therapeutic improvements in fibrosis
- The primary analysis of REGENERATE showed a significant improvement in fibrosis and NASH with OCA based on biopsy; in this secondary analysis, we evaluate the potential utility of 5 different NITs in monitoring NASH patients with fibrosis during treatment with OCA

MATERIAL/MÉTODOS

STUDY DESIGN AND PATIENTS

- Patients were randomized (1:1:1) to placebo, OCA 10 mg, or OCA 25 mg once daily (QD) (**Figure 1**)
- Randomization was stratified by type 2 diabetes at enrollment and use of thiazolidinediones/glitazones or vitamin E at baseline

Figure 1. Study Design



EOS, end of study.
Study details, including key inclusion/exclusion criteria have been previously disclosed.[4]

BIOPSIES

- Biopsies were centrally read at baseline and Month 18 by expert pathologists blinded to treatment assignment

NONINVASIVE ASSESSMENTS

- Assessments included commonly used markers of liver fibrosis and definite NASH
  - Fibrosis-4 (FIB-4) index[6]
  - APRI (aspartate aminotransferase [AST] to platelet ratio index)[7]
  - FibroSURE®[8]
  - Cytokeratin-18 (CK-18) M30 fragment[9]
  - Liver stiffness via vibration-controlled transient elastography (VCTE)[10]
    - Measured using the FibroScan® VCTE device in a subset of patients

STATISTICAL ANALYSES

- Least square (LS) mean change from baseline and standard error (SE) over time were analyzed using a mixed-effect repeated measures (MMRM) model with treatment, baseline, visit, visit by treatment interaction, and stratification factors (baseline diabetes status and use of thiazolidinediones or vitamin E) included in the model
- P values are based on the MMRM model
- Month 18 fibrosis status was classified into 3 categories: 1) Improvement of Fibrosis by ≥1 Stage, 2) No Change in Fibrosis Stage, and 3) Worsening of Fibrosis by ≥1 Stage
- Analysis of NIT changes over time against Month 18 fibrosis status was conducted in the intent-to-treat (ITT) population with non-missing values in both fibrosis stage and NIT values
- The ITT population included patients with fibrosis stage F2-F3 who had received ≥1 dose of treatment and reached, or would have reached, the Month 18 visit by the pre-specified interim analysis cutoff date

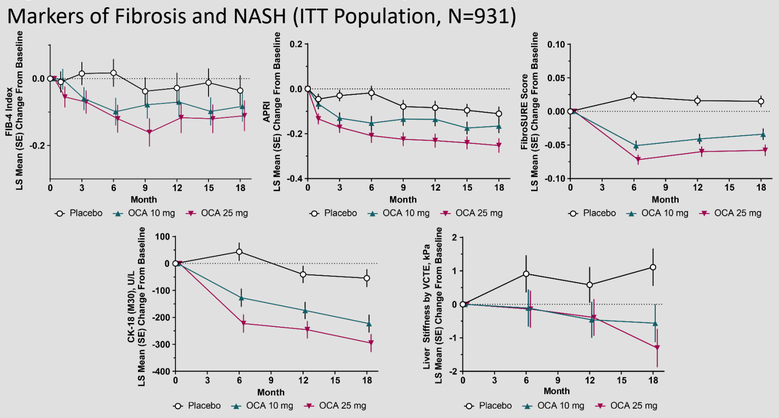
RESULTADOS

Table. Demographic and Baseline Clinical Characteristics (ITT Population, N=931)

Characteristics	Placebo (n=311)	OCA 10 mg (n=312)	OCA 25 mg (n=308)
Age, years, mean (SD)	55 (12)	55 (11)	55 (11)
Female, n (%)	187 (60)	177 (57)	175 (57)
White, n (%)	264 (94)	263 (92)	249 (87)
Hispanic ethnicity, n (%)	52 (18)	42 (15)	47 (17)
Fibrosis stage F3, n (%)	169 (54)	182 (58)	169 (55)
NAS ≥6, n (%)	215 (70)	211 (68)	208 (68)
Laboratory parameters, mean (SD)			
ALT, U/L	80 (57)	76 (47)	80 (56)
AST, U/L	59 (41)	57 (34)	57 (34)
Platelet count, × 10^9/L	241.9 (67.0)	238.5 (68.0)	237.2 (69.0)
Total bilirubin, mg/dL	0.64 (0.3)	0.65 (0.3)	0.69 (0.3)
Noninvasive markers, mean (SD)			
FIB-4	1.62 (0.9)	1.63 (0.9)	1.63 (0.9)
APRI	0.78 (0.6)	0.76 (0.5)	0.79 (0.6)
FibroSURE	0.40 (0.2)	0.42 (0.2)	0.43 (0.2)
CK-18 (M30), U/L	776.5 (802.1)	713.6 (617.9)	733.5 (745.8)
Liver stiffness by VCTE, kPa	12.46 (7.5)	11.94 (5.6)	12.36 (7.3)

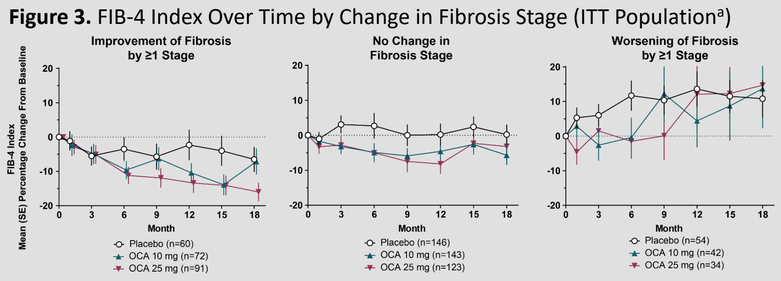
ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAS, NAFLD activity score; SD, standard deviation.

Figure 2. OCA Induces Time- and Dose-Dependent Improvements in Noninvasive Markers of Fibrosis and NASH (ITT Population, N=931)



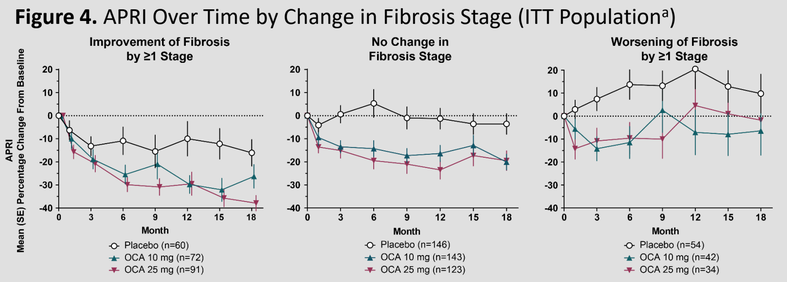
*p<0.05; **p<0.01; ***p<0.001 (p value for OCA 10 mg or OCA 25 mg versus placebo at Month 6 and Month 18)

Figure 3. FIB-4 Index Over Time by Change in Fibrosis Stage (ITT Population[a])



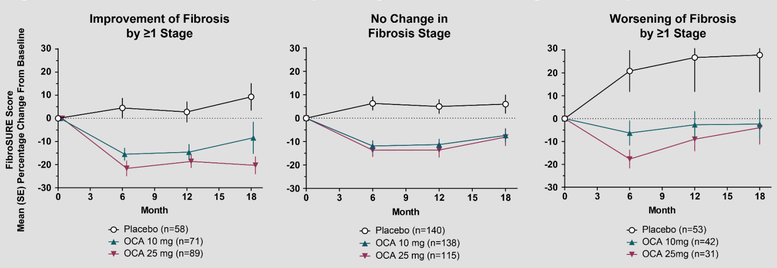
[a]ITT population with available Month 18 or End of Treatment data, N=777.

Figure 4. APRI Over Time by Change in Fibrosis Stage (ITT Population[a])



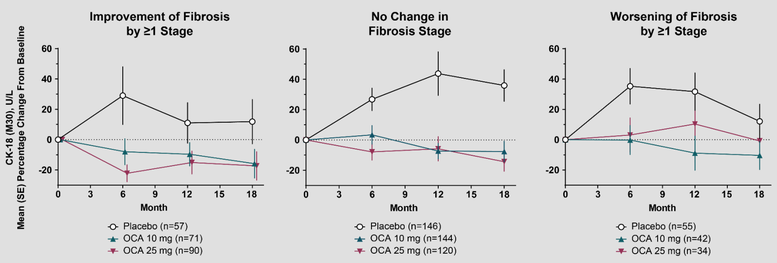
[a]ITT population with available Month 18 or End of Treatment data, N=777.

Figure 5. FibroSURE Over Time by Change in Fibrosis Stage (ITT Population[a])



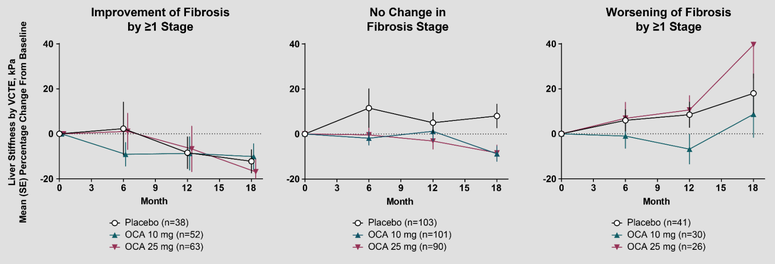
[a]ITT population with available Month 18 or End of Treatment data, N=777.

Figure 6. CK-18 (M30) Levels Over Time by Change in Fibrosis Stage (ITT Population[a])



[a]ITT population with available Month 18 or End of Treatment data, N=777.

Figure 7. Liver Stiffness (VCTE) Over Time by Change in Fibrosis Stage (ITT Population[a])



[a]ITT population with available Month 18 or End of Treatment data, and available TE data, N=559 (patients with median liver stiffness values out of range [ie, <1.5 kPa and >75 kPa] were excluded).

CONCLUSÕES

- Consistent with observed histologic improvements in fibrosis and NASH with OCA, OCA treatment improves NITs of fibrosis and NASH in a time- and dose-dependent manner, consistent with its demonstrated antifibrotic benefit on biopsy
  - Rapid improvements were observed in both serum-based NITs (eg, FIB-4 and FibroSURE) and imaging NITs (eg, VCTE by FibroScan®) as early as 3 months and sustained through 18 months
  - OCA also robustly improves serum CK-18, a marker of apoptosis that associates with fibrosing steatohepatitis, consistent with OCA-mediated histologic resolution of definite NASH based on pathologist diagnostic assessment[4]
- NIT changes mirror shifts in fibrosis stage, with greatest improvements observed in patients with ≥1 fibrosis stage reduction
  - In contrast to those receiving placebo, OCA-treated patients with no change in fibrosis stage also had marked improvement in NITs, suggesting the therapeutic benefit of OCA is not adequately captured by categorical fibrosis staging at Month 18
  - Sustained improvement in NITs suggests the potential for additional histologic improvement with longer-term treatment (as observed in patients with viral hepatitis who had long-term sustained response)[11]
- These data support the use of easily accessible noninvasive markers of fibrosis and steatohepatitis to monitor NASH patients treated with OCA
- The REGENERATE Month 18 interim analysis results are based on surrogate endpoints considered reasonably likely to predict clinical benefit, and longer-term OCA treatment effect on clinical outcomes has not yet been demonstrated: the study is ongoing through outcomes to characterize OCA's clinical benefit

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CLINICAL TRIAL INFORMATION

ClinicalTrials.gov: NCT02548351

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