REGENERATE
NASH FIBROSIS STUDY

Obeticholic Acid Treatment in Patients with Non-alcoholic Steatohepatitis: A Secondary Analysis of the REGENERATE Study Across Fibrosis Stages

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Disclosures

Consulting: Novartis, Pfizer, Lilly, Novo Nordisk, Sanofi, Gilead, Conatus, Tern, Hemoshear, Glympse, Bird Rock, Blade, Teva, Echosens, Prosciento, ARTham, MedImmune, AstraZeneca, Salix, and NASH Pharmaceuticals

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Ownership: Sanyal Bio

Stock shareholder/options: Genfit, Indalo, Tiziana, Durect, Exalenz, and Galmed

Scientific advisor: Albireo, AstraZeneca, and MedImmune

Background

- NASH is a major cause of liver-related morbidity and mortality[1]
- Liver-related mortality increases in patients with NASH with advancing fibrosis[2], making improvement in fibrosis a key therapeutic objective
- There are currently no approved pharmacological therapies for NASH
- Obeticholic acid (OCA), a potent and selective FXR agonist, improved liver histology in a Phase 2 trial (FLINT) of patients with NASH[3]
- These results led to the pivotal REGENERATE Phase 3 study; top-line results of the interim analysis in NASH patients with fibrosis stage 2 or 3 (Primary ITT Population) were reported at the 2019 International Liver Congress™[4]

FXR, farnesoid X receptor; ITT, intent-to-treat; NASH, non-alcoholic steatohepatitis, OCA, obeticholic acid.

1. Angulo P, et al. *Gastroenterology*. 2015;149:389-397; 2. Dulai PS, et al. *Hepatology*. 2017;65(5):1557-1565; 3. Neuschwander-Tetri BA, et al. *Lancet.* 2015;385:956-965. 4. Younossi ZM, et al. *J Hepatol*. 2019;70(suppl 1):e5.

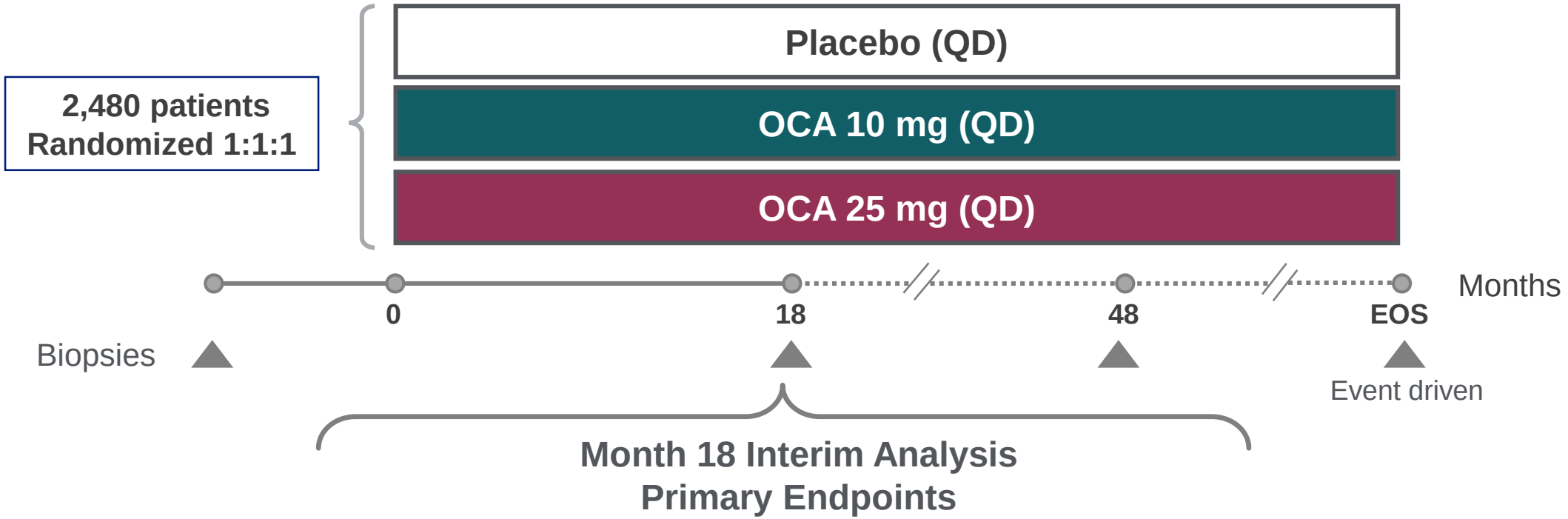
Objective

Prespecified REGENERATE secondary analysis of the effect of OCA in the Expanded ITT Population*

- Patients with fibrosis stages 2 and 3
- Patients with fibrosis stage 1 at increased risk of disease progression due to co-morbidities[1]
  - Comorbidities included type 2 diabetes, obesity (BMI ≥30 kg/m^2) or ALT >1.5 × ULN

* Expanded ITT Population has also been referred to as the Full Efficacy Population
ALT, alanine aminotransferase
1. Benedict M, et al. *World J Hepatol*. 2017;9(16):715-732.

REGENERATE Study Design



Study success was defined as achievement of one of these two primary endpoints

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The interim analysis was conducted after 931 randomized patients with fibrosis stage 2 or 3 had or would have reached their actual/planned Month 18 visit (ITT Population).
EOS analysis of clinical outcomes to confirm clinical benefit.
EOS, end of study; QD, once a day.

Study Eligibility Criteria

KEY INCLUSION CRITERIA

- Biopsy-confirmed NASH
- Fibrosis stage 2 or 3 (NASH CRN)
  - Exploratory cohort with fibrosis stage 1 and concomitant risk factors[a]
- NAFLD activity score (NAS) ≥4

KEY EXCLUSION CRITERIA

- Evidence of other chronic liver disease
- Histologic presence of cirrhosis
- Total bilirubin >1.5 mg/dL
- ALT ≥10 × ULN
- HbA1c >9.5%
- Significant alcohol consumption[b]

All biopsies were read centrally and at Month 18 biopsy slides were pair-read ensuring that pathologists were blinded to both treatment assignment and biopsy sequence

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[a]Risk factors included type 2 diabetes, obesity (BMI ≥30 kg/m^2) or ALT >1.5 × ULN.
[b]Defined as >2 units/day for females and >4 units/day for males for >3 months within 1 year before screening.
BMI, body mass index; CRN, clinical research network; HbA1c, glycated hemoglobin; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; ULN, upper limit of normal.

Prespecified Populations

Population	N	Definition
Primary Intent to Treat Previously presented[1]	931	Patients with stage 2 or 3 fibrosis who received at least 1 dose of study treatment enrolled by predefined cut-off date
Expanded Intent to Treat	**1,218**	**All interim analysis cohort patients randomized by the predefined cutoff date, including all fibrosis stages (stages 1, 2, and 3), who received at least 1 dose of study treatment**
Safety	1,968	All patients (with stage 1, 2, or 3 fibrosis) who received at least 1 dose of study treatment

1. Younossi ZM, et al. *J Hepatol*. 2019;70(suppl 1):e5.

Patient Disposition

Expanded ITT Population, N=1,218

Disposition, n (%)	Placebo (n=407)	OCA 10 mg (n=407)	OCA 25 mg (n=404)
Completed Month 18 biopsy	330 (81)	328 (81)	320 (79)
Study discontinuation	62 (15)	73 (18)	64 (16)
Treatment discontinuation	92 (23)	94 (23)	107 (26)
Withdrawal of consent	32 (8)	30 (7)	21 (5)
Death	1 (<1)	0	0
Adverse event	29 (7)	27 (7)	60 (15)
Physician decision	3 (<1)	3 (<1)	9 (2)
Lost to follow-up	10 (2)	11 (3)	6 (1)

Demographic and Baseline Characteristics

Expanded ITT Population

Characteristics	Placebo (n=407)	OCA 10 mg (n=407)	OCA 25 mg (n=404)
Age, years, mean (SD)	54 (12)	54 (11)	54 (12)
Female, n (%)	231 (57)	230 (57)	233 (58)
White, n (%)	338 (93)	343 (91)	325 (87)
Hispanic ethnicity, n (%)	65 (18)	63 (17)	63 (17)
Fibrosis stage 1, n (%)	96 (24)	95 (23)	96 (24)
NAS ≥6, n (%)	256 (63)	259 (64)	258 (64)
Type 2 diabetes,[a] n (%)	220 (54)	219 (54)	224 (55)
Laboratory parameters, mean (SD)			
ALT, U/L	79 (55)	75 (48)	80 (58)
AST, U/L	57 (38)	54 (33)	55 (35)
Concomitant medication use			
Lipid lowering, n (%)	230 (57)	217 (53)	212 (52)
Statins, n (%)	186 (46)	178 (44)	170 (42)
Antidiabetic medication, n (%)	212 (52)	221 (54)	211 (52)
TZD,[a] n (%)	5 (1)	9 (2)	5 (1)
Vitamin E,[a] n (%)	52 (13)	44 (11)	46 (11)

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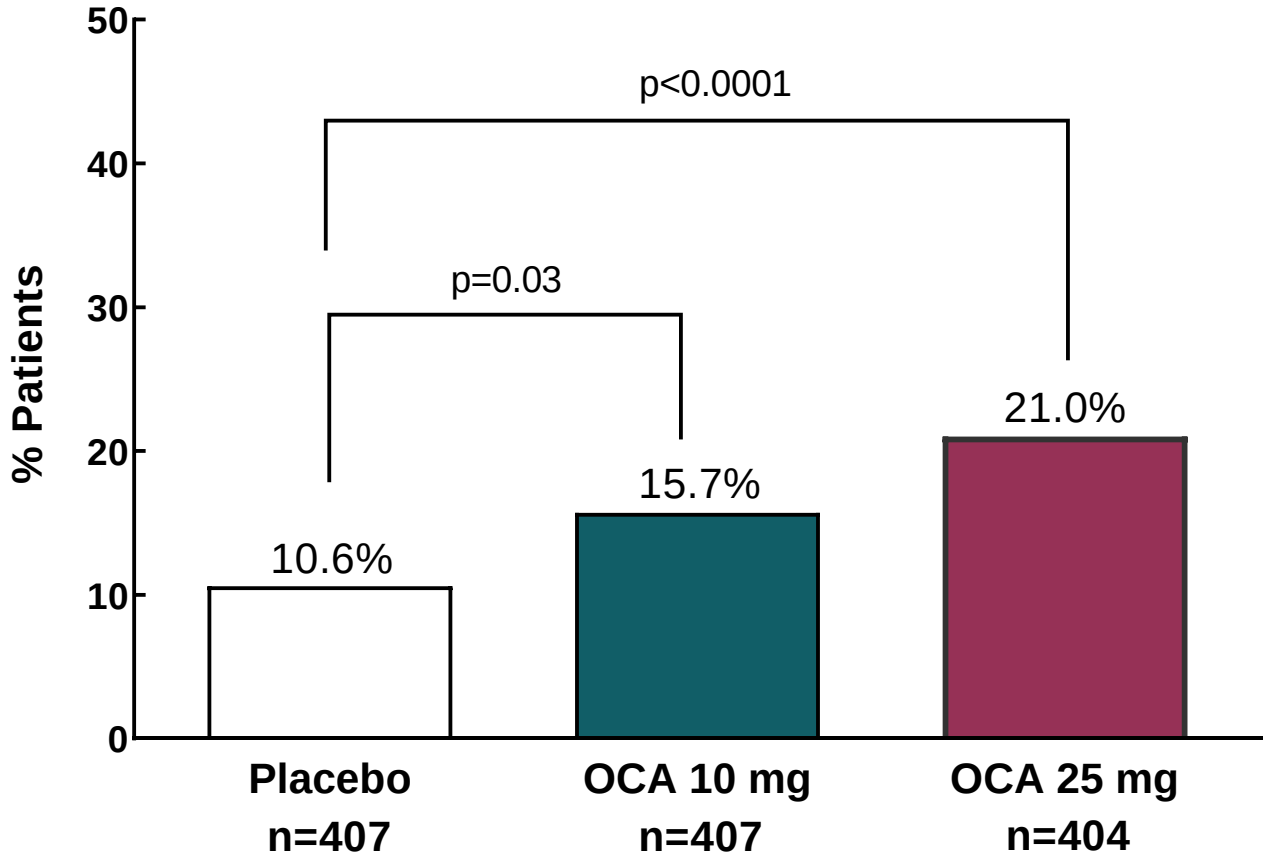
Expanded ITT Population, N=1,218.
[a]Randomization was stratified based on presence of type 2 diabetes and treatment with glitazones (TZDs) or Vitamin E.
AST, aspartate transaminase; SD, standard deviation; TZD, thiazolidinediones; U/L, units per liter.

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH

Primary Endpoint: Expanded ITT Population

- The results in the Expanded ITT Population are similar to those observed in the Primary ITT analysis of patients with fibrosis stage 2 or 3



Expanded ITT Population, N=1,218.
Primary endpoint definition: Fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis).
This primary endpoint was met in the Primary ITT Population.
P values are nominal.

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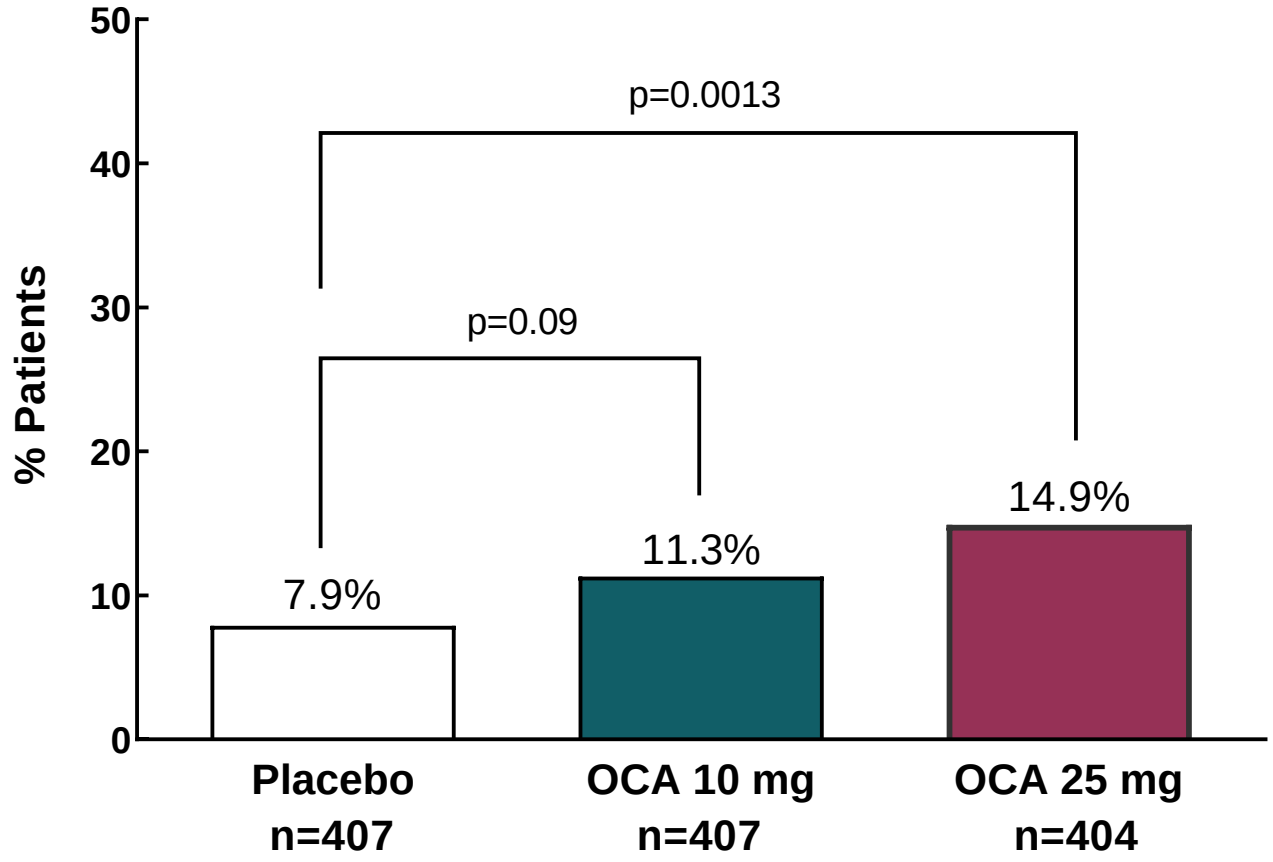
NASH Resolution with No Worsening of Fibrosis

Additional Primary Endpoint: Expanded ITT Population



Expanded ITT Population, N=1,218.
Primary endpoint definition: (i) overall pathologist diagnostic assessment of “no steatohepatitis,” and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1, and (iii) no increase in fibrosis stage from baseline.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Primary ITT Population in the Month 18 interim analysis
P values are nominal.

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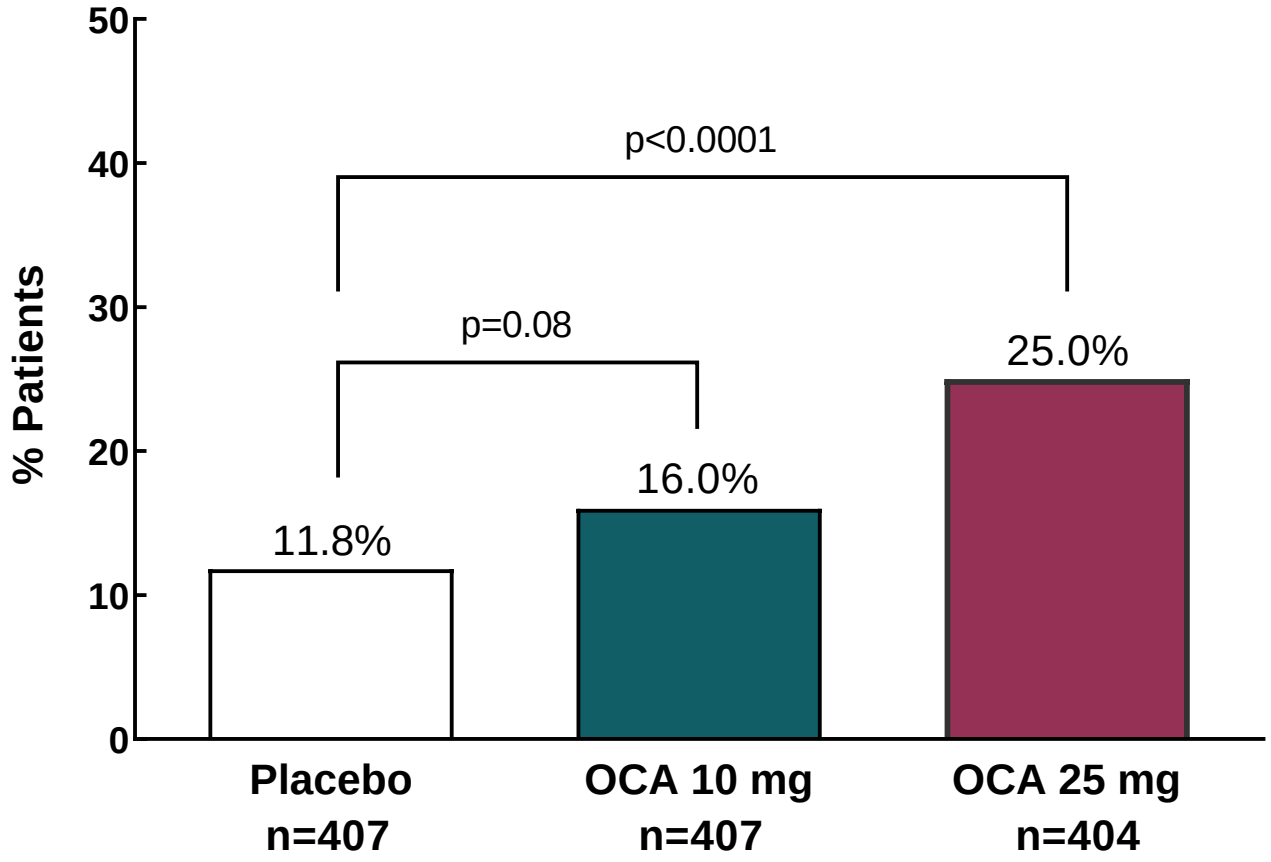
Resolution of Definite NASH with No Worsening of Fibrosis

Pathologist Diagnostic Assessment: Expanded ITT Population[a]



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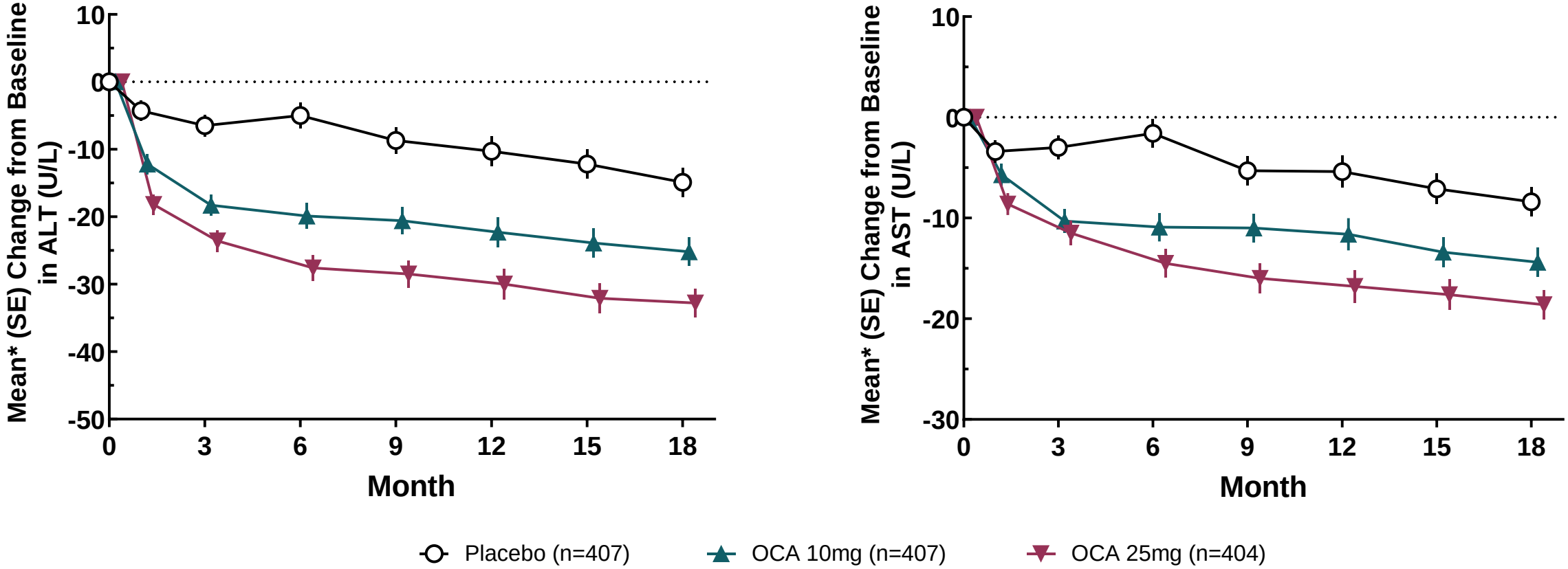
Expanded ITT Population, N=1,218. .
[a]Post-hoc analysis with endpoint defined as: (i) overall pathologist diagnostic assessment of “no steatohepatitis,” and (ii) no increase in fibrosis stage from baseline.
P values are nominal.

Changes From Baseline in ALT and AST Over Time

Expanded ITT Population



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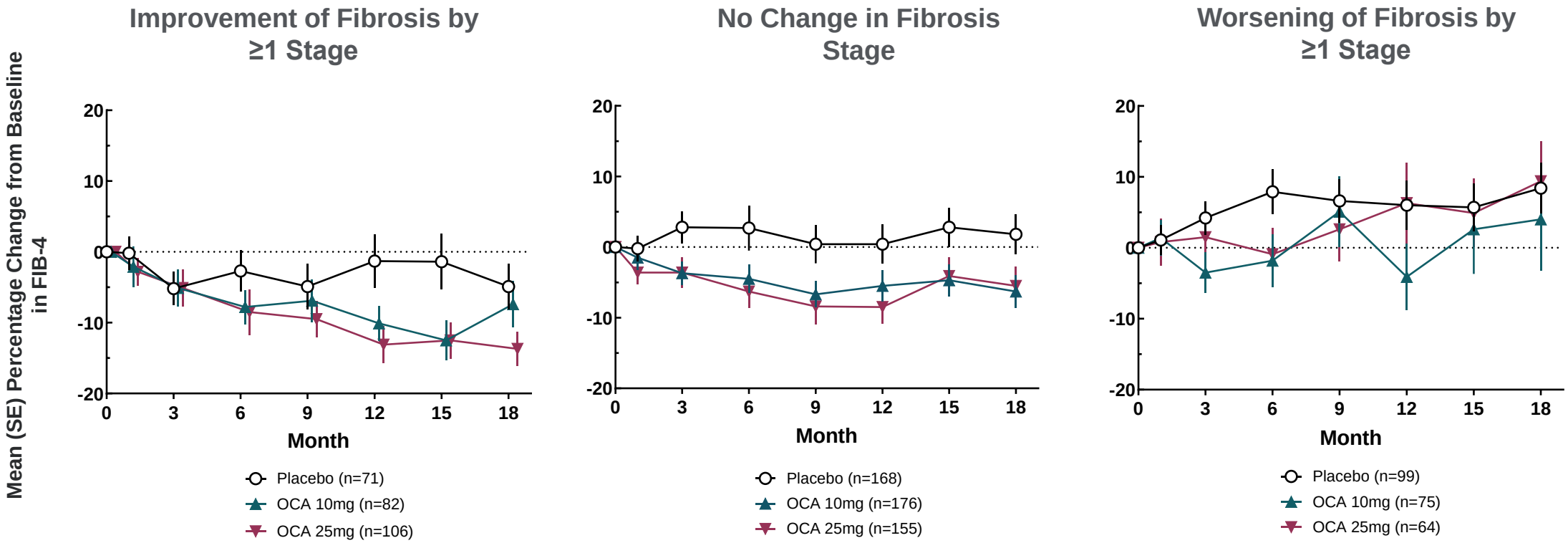
Expanded ITT Population, N=1,218.
*Least square mean
SE, standard error.

Percent Change in FIB-4 Scores Over Time by Fibrosis Responder Status*

Expanded ITT Population, Completers

- For this analysis, expanded ITT completers were used as 2 completed biopsies were necessary to assure change in fibrosis stage



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Expanded ITT Population, Completers only to assure we have 2 biopsies
*≥1 stage improvement in fibrosis, no change in fibrosis stage, ≥1 stage worsening in fibrosis
SE, standard error.

Safety and Tolerability

Safety Population, N=1,968

Overall safety profile

- Pruritus was the most frequent AE (19% placebo, 28% OCA 10 mg, 51% OCA 25 mg)
- Frequency of SAEs was similar across groups (11-14%)
- Three deaths, unrelated to treatment, occurred on study (placebo, n=2; OCA 25 mg, n=1)

Hepatobiliary

- Gallstone-related AEs occurred at a rate of <1%, 1% and 3% in placebo, OCA 10 mg and OCA 25 mg patients, respectively
- Pancreatitis, a more serious and potentially gallstone-related event, was rare and evenly distributed across treatment groups (incidence <1% in all treatment groups)
- Hepatic SAEs were rare (<1% in all treatment groups). While more occurred in the OCA 25 mg group, there was no pattern attributable to OCA and all cases were associated with confounding severe intercurrent illness and/or concomitant medications

Safety Population defined as all randomized patients with fibrosis stage 1, 2, or 3 who received at least 1 dose of study treatment.
AEs, adverse events; SAEs, serious adverse events

Safety and Tolerability

Safety Population

Lipids and Cardiovascular

- In patients receiving OCA, low-density lipoprotein cholesterol (LDLc) increased by month 1 and decreased thereafter, approaching baseline by month 18
- Statin therapy was initiated in 10% of placebo patients and 24% of each OCA treatment arm. Among OCA patients who initiated statins, LDLc increases reversed and fell to below baseline levels by month 6
- Incidence of cardiovascular AEs and SAEs was similar across the treatment groups (AEs: 5% placebo, 7% OCA 10 mg, and 6% OCA 25 mg; SAEs 2% placebo, 1% OCA 10 mg, 2% OCA 25 mg)

Glycemic Parameters

- In patients with type 2 diabetes, OCA treatment was associated with an early transient increase in glucose and HbA1c with return to levels similar to placebo by month 6
- No clinically meaningful changes were noted in non-diabetic patients

Safety Population, N=1,968.
HbA1c, hemoglobin A1c; LDLc, low density lipoprotein-cholesterol

Secondary Analysis of the REGENERATE Data in the Expanded ITT Population

Summary and Conclusion

- After 18 months of treatment, OCA improved liver fibrosis in the Expanded ITT Population, demonstrating consistent efficacy with the primary study results
- Treatment with OCA also improved steatohepatitis and liver biochemistry in patients with NASH and fibrosis stage 1 to 3
- AEs were mostly mild to moderate; the most common were consistent with the known profile of OCA
- The REGENERATE month 18 interim analysis results are based on surrogate endpoints considered reasonably likely to predict clinical benefit
  - 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

Acknowledgments

We are grateful to the patients and their families, the investigators, and the healthcare providers who are participating in the ongoing REGENERATE study across ~350 sites in 20 countries