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Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial

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Supplementary Appendix

Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis— Interim Analysis From a Multicentre, Randomised, Placebo-Controlled Phase 3 Study

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SUPPLEMENTAL METHODS

Study Design

Based on the FLINT results, Intercept received Breakthrough Therapy designation for OCA for "the treatment of NASH with liver fibrosis", a serious condition with currently no available therapies. The Phase 3 development program, specifically the study design, patient population, and study endpoints of the single pivotal Phase 3 study (study 747-303 [REGENERATE]), was agreed upon in a series of collaborative interactions with the FDA and other regulatory authorities. The study design originated from the FDA-American Association for the Study of Liver Diseases workshop report in 2015 and endpoints were reflective of the clinical research completed at that time.

At initiation in 2015, approximately 2065 patients were targeted for enrolment with a planned interim analysis occurring when approximately 1400 fibrosis stage 2 or 3 patients completed 18 months of treatment. The month 18 interim analysis was originally established as a "co-primary endpoint" and was powered based on a fibrosis primary endpoint definition where "no worsening of NASH" was defined as no worsening of hepatocellular ballooning or lobular inflammation and did not take into account steatosis. The original definition of NASH resolution was based on overall histopathological interpretation with no worsening of fibrosis.

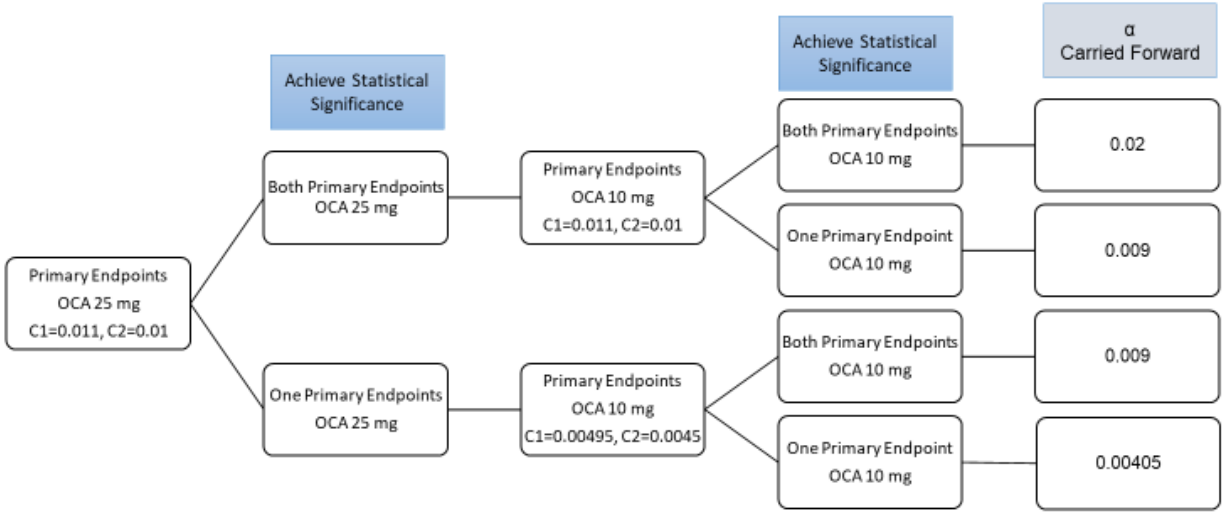
In 2017, considerations for NASH clinical trial endpoints evolved and, in agreement with the FDA, the study design was amended to reflect two primary endpoints as well as an updated definition of NASH resolution based on scores of hepatocellular ballooning (0) and lobular inflammation (0-1) for the month 18 interim analysis. This is what led to the revised sample size. Based on results from the FLINT study, the effect size based on this objective definition was larger and allowed for a small sample size to detect NASH resolution. The overall sample size increased to include approximately 2400 patients targeted for enrolment with the planned month 18 interim analysis occurring when at least 750 patients with fibrosis stage 2 or 3 would have reached their month 18 visit.

More information regarding the dosing and endpoint rationale can be found in Ratziu V, et al. *Contemp Clin Trials*. 2019;84:105803 and a summary of protocol changes can be located on clinicaltrials.gov (NCT02548351).

Statistical Analysis: Histological Primary Endpoints

Inferential testing of the primary endpoints at month 18 were communicated and agreed upon with the FDA in 2018 prior to database lock of the interim analysis.

The 2-sided Type I error (alpha) allocated to all testing in this single study will be 0.05. The histological endpoints at the month 18 interim analysis reported in this manuscript was performed with an alpha level of 0.02. The primary clinical outcomes composite endpoint (at study completion) will be tested with an alpha level of 0.03. As shown in the figure, the inferential testing started with the two primary endpoints in comparing the OCA 25 mg dose group versus placebo using the Truncated-Hochberg procedure (Gamma=0.1) and Type I error of 0.02.



All Tests using Truncated Hochberg with gamma=0.1

One Primary Endpoint Achieves Statistical Significance at the OCA 25 mg Dose Level

- Primary Endpoints at the OCA 25 mg Dose Level:
  - If the larger p-value was greater than 0.011 but the smaller p-value was < 0.01 then only one of the two primary efficacy endpoints achieved statistical significance in favor of the OCA 25 mg group. Preserved alpha of 0.009 would be carried to compare placebo and OCA 10 mg groups with respect to the primary endpoints using the Truncated Hochberg procedure (Gamma = 0.1).
- Primary Endpoints at the OCA 10 mg Dose Level:
  - Placebo and OCA 10 mg groups were compared, using the Truncated Hochberg procedure, with respect to the fibrosis and NASH primary efficacy endpoints with critical values of 0.00495 and 0.0045 against which the larger and smaller p-value were compared respectively.
- Key Secondary Endpoint at the OCA 25 mg Dose Level:
  - Placebo and OCA 25 mg groups were compared with respect to the key secondary endpoint sequentially after the primary endpoint at OCA 10 mg dose level.
- Key Secondary Endpoint at the OCA 10 mg Dose Level:
  - Placebo and OCA 10 mg groups were compared with respect to the key secondary endpoint sequentially after the key secondary endpoint at OCA 25 mg dose level.

Study Inclusion/Exclusion Criteria

Subject Inclusion Criteria

1. Histologic evidence of NASH upon central read of a liver biopsy obtained no more than 6 months before Day 1 defined by presence of all 3 key histological features of NASH with a score of at least 1 for each and a combined score of 4 or greater out of a possible 8 points according to NASH CRN criteria.
2. Histologic evidence of fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging fibrosis) as defined by the NASH CRN scoring of fibrosis, or
   Histologic evidence of fibrosis stage 1a or stage 1b (mild or moderate, zone 3 perisinusoidal) as defined by the NASH CRN scoring of fibrosis if accompanied by ≥1 of the following risk factors:
   - Obesity (BMI ≥30 kg/m^2)
   - Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c [HbA1c] ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test, or random plasma glucose ≥200 mg/dL)
   - ALT >1.5× ULN.
3. For subjects with a historical biopsy, is either not taking or is on stable doses of TZDs/glitazones or vitamin E for 6 months before Day 1.
4. Stable body weight (ie, not varying by >10% for at least 3 months) before Day 1.
5. Age ≥18 years.
6. Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, condom (male or female) with spermicide or diaphragm with spermicide
   - Intrauterine device
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence (defined as refraining from heterosexual intercourse).
7. Must provide written informed consent and agree to comply with the study protocol.

Subject Exclusion Criteria

Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization.

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Screening (significant alcohol consumption is defined as more than 2 units/day for females and more than 4 units/day for males, on average).
2. Prior (at any point) or planned (during the study period) ileal resection, or prior (within 5 years before Screening) or planned (during the study period) bariatric surgery (eg, gastric bands, gastroplasty, roux-en-Y gastric bypass).
3. HbA1c >9.5% within 60 days before Day 1.
4. Evidence of other forms of known chronic liver disease including:
   - Positive test result at Screening for hepatitis B surface antigen (HBsAg)

- Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result
- PBC, PSC, autoimmune hepatitis, or overlap syndrome
- Alcoholic liver disease
- Wilson's disease, hemochromatosis, or iron overload
- Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal [LLN] or exclusion at the Investigator's discretion)
- Prior known drug-induced liver injury within 5 years before Day 1
- Known or suspected HCC
- History of liver transplant, current placement on a liver transplant list, or MELD score >12.

5. Histological presence of cirrhosis.
6. Total bilirubin >1.5 mg/dL (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is <1.5× ULN).
7. Conjugated bilirubin ≥1.5 x ULN.
8. AST or ALT ≥10× ULN, international normalized ratio (INR) ≥1.4, or serum creatinine ≥1.5 mg/dL.
9. Creatine phosphokinase >5x ULN.
10. Platelet count <100 000/mm^3.
11. LDL ≥190 mg/dL and already on a stable dose of statin and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for ≥30 days at Screening.
12. Inability to safely undergo a liver biopsy.
13. History of biliary diversion.
14. Known positivity for human immunodeficiency virus infection.
15. Previous exposure to OCA.
16. Acute cholecystitis or acute biliary obstruction.
17. BMI >45 kg/m^2

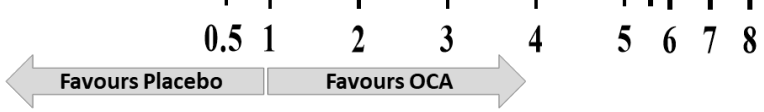
Supplementary Table S1: Demographic and baseline clinical characteristics (per-protocol population, N=668)

Characteristics	Placebo (n=224)	OCA 10 mg (n=226)	OCA 25 mg (n=218)
Age, years, mean (SD)	55 (12)	55 (11)	54 (12)
Female	133 (59%)	126 (56%)	122 (56%)
White*	189 (94%)	192 (94%)	185 (89%)
Hispanic ethnicity†	29 (14%)	29 (14%)	33 (16%)
Fibrosis stage F3	122 (54%)	135 (60%)	117 (54%)
NAS ≥6	159 (72%)	152 (67%)	144 (66%)
Type 2 diabetes‡	120 (54%)	121 (54%)	119 (55%)
Weight, mean kg (SD)	96 (19)	94 (19)	97 (20)
Laboratory parameters, mean (SD)			
ALT, U/L	77 (53)	73 (44)	82 (61)
AST, U/L	57 (38)	55 (31)	56 (34)
Concomitant medication use			
Lipid lowering§	131 (58%)	128 (57%)	113 (52%)
Statins	108 (48%)	108 (48%)	86 (39%)
Antidiabetic medication	117 (52%)	120 (53%)	111 (51%)
Thiazolidinedones‡	3 (1%)	8 (4%)	2 (<1%)
Vitamin E*	29 (13%)	25 (11%)	23 (11%)

Data are n (%), unless otherwise stated. ALT=alanine aminotransferase. AST=aspartate aminotransferase. NAS=NAFLD activity score. PCSK9=proprotein convertase subtilisin-kexin type 9. SD=standard deviation.
*Percentages calculated based on patients for whom race information was not missing.
†Percentages calculated based on patients for whom ethnicity information was not missing.
§In addition to statins, lipid lowering drugs included fibrates, cholesterol-absorbing resins, PCSK9 inhibitors, and omega-3 fatty acids.
‡Randomisation was stratified based on presence of type 2 diabetes and treatment with thiazolidinediones or vitamin E.

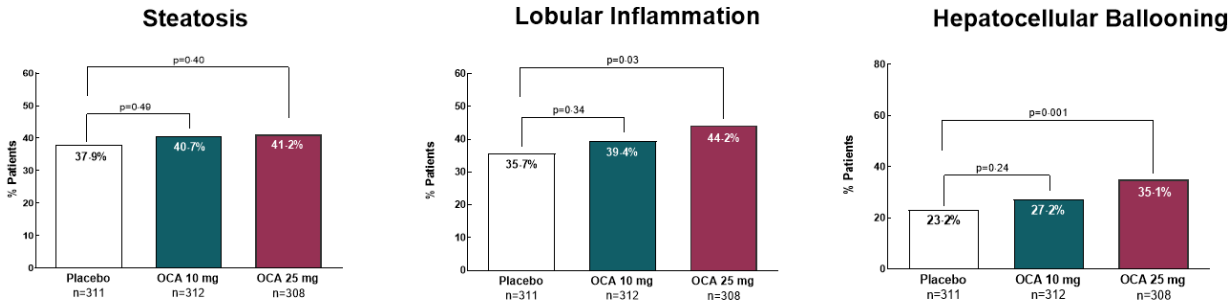
Supplementary Figure S1: Subgroup analysis of fibrosis improvement by ≥1 stage with no worsening of NASH. Treatment response ratio and 95% confidence intervals of obeticholic acid versus placebo for patients in the ITT population grouped by fibrosis stage, NAFLD Activity Score (NAS), presence of type 2 diabetes at baseline, age, gender and use of vitamin E or TZD at baseline[a]. A response ratio greater than 1 favours obeticholic acid.

Subgroups	OCA : Placebo Response Ratio (95% CI)	OCA vs Placebo	p-Value
Fibrosis Stage 2			
OCA 25-mg (n=139)	2·0 (1·2, 3·3)		p<0·01
OCA 10-mg (n=130)	1·5 (0·9, 2·6)		0·14
Fibrosis Stage 3			
OCA 25-mg (n=169)	1·8 (1·1, 3·0)		0·02
OCA 10-mg (n=182)	1·5 (0·9, 2·5)		0·13
NAS ≥6			
OCA 25-mg (n=208)	2·1 (1·4, 3·2)		p<0·01
OCA 10-mg (n=211)	1·5 (1·0, 2·3)		0·08
NAS <6			
OCA 25-mg (n=100)	1·6 (0·8, 3·3)		0·20
OCA 10-mg (n=101)	1·5 (0·7, 3·3)		0·30
Type 2 Diabetes			
OCA 25-mg (n=171)	2·0 (1·1, 3·6)		0·02
OCA 10-mg (n=171)	1·8 (1·0, 3·4)		0·04
No Type 2 Diabetes			
OCA 25-mg (n=137)	1·9 (1·2, 3·0)		p<0·01
OCA 10-mg (n=141)	1·2 (0·7, 2·0)		0·42
Age <65 years			
OCA 25-mg (n=251)	1·9 (1·3, 2·8)		p<0·01
OCA 10-mg (n=249)	1·4 (0·9, 2·2)		0·10
Age ≥65 years			
OCA 25-mg (n=57)	2·6 (1·1, 6·1)		0·03
OCA 10-mg (n=63)	1·7 (0·6, 4·6)		0·27
Male			
OCA 25-mg (n=133)	1·9 (1·1, 3·4)		0·03
OCA 10-mg (n=135)	1·7 (0·9, 3·0)		0·08
Female			
OCA 25-mg (n=175)	2·0 (1·3, 3·2)		p<0·01
OCA 10-mg (n=177)	1·3 (0·8, 2·2)		0·26
Vitamin E or TZD use: Yes			
OCA 25-mg (n=39)	2·1 (0·8, 5·6)		0.14
OCA 10-mg (n=48)	2·9 (1·1, 7·5)		0.02
Vitamin E or TZD use: No			
OCA 25-mg (n=269)	1·9 (1·3, 2·8)		p<0.01
OCA 10-mg (n=264)	1·3 (0·8, 1·9)		0.31

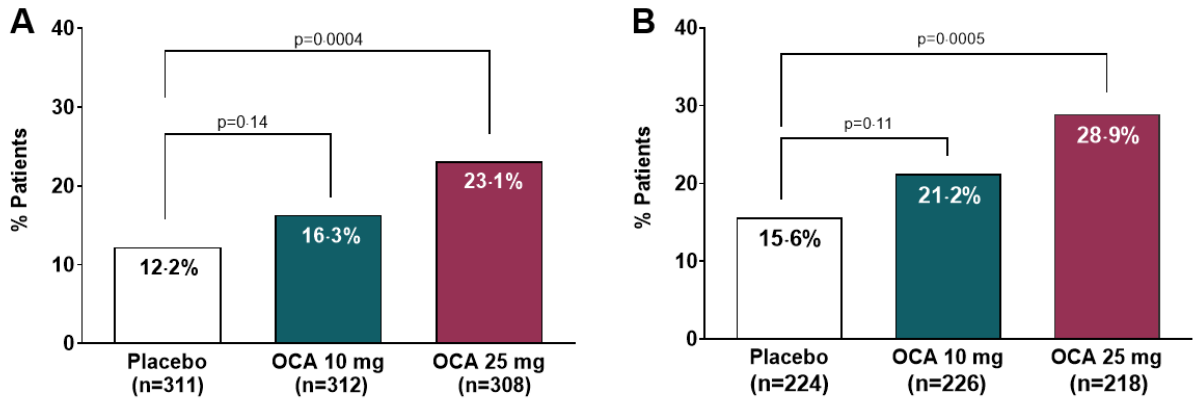


[a] There were too few nonwhite patients to make a meaningful comparison based on race.

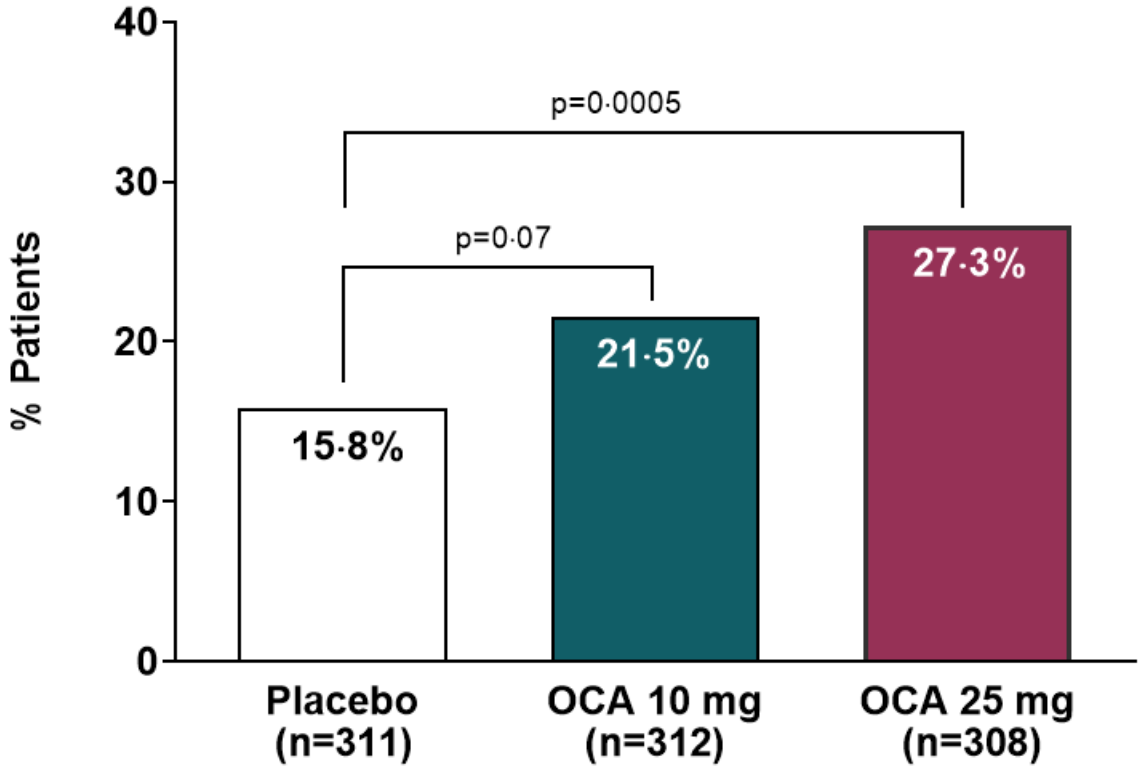
Supplementary Figure S2: Improvements in histologic features of NASH (steatosis, lobular inflammation, and hepatocellular ballooning). The proportion of patients with improvements in histologic features of NASH (steatosis, lobular inflammation, and hepatocellular ballooning) in the ITT population.



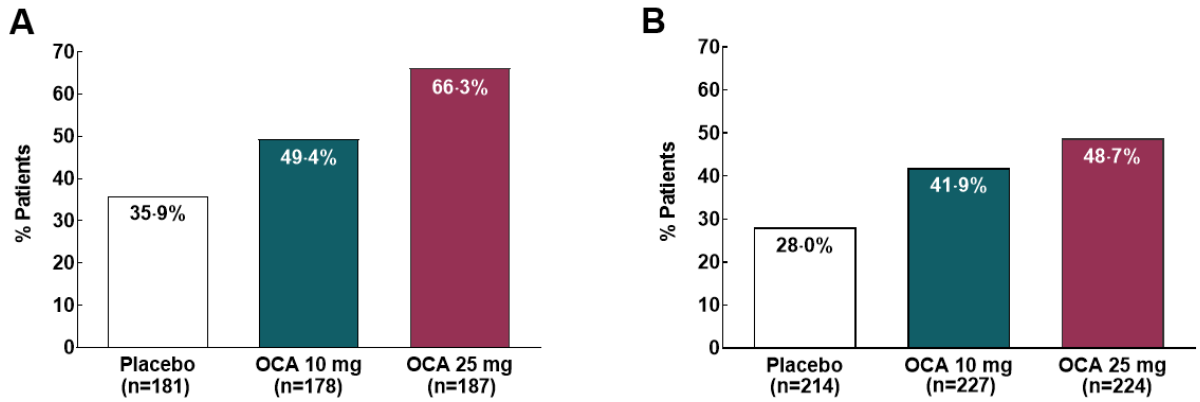
Supplementary Figure S3: Pathologist diagnostic assessment of NASH: Resolution of NASH with no worsening of fibrosis based on the absence of definite steatohepatitis. The proportion of patients with resolution of NASH with no worsening of fibrosis, based on the pathologist diagnostic assessment of the absence of definite steatohepatitis in the ITT (Panel A) and per protocol (Panel B) populations.



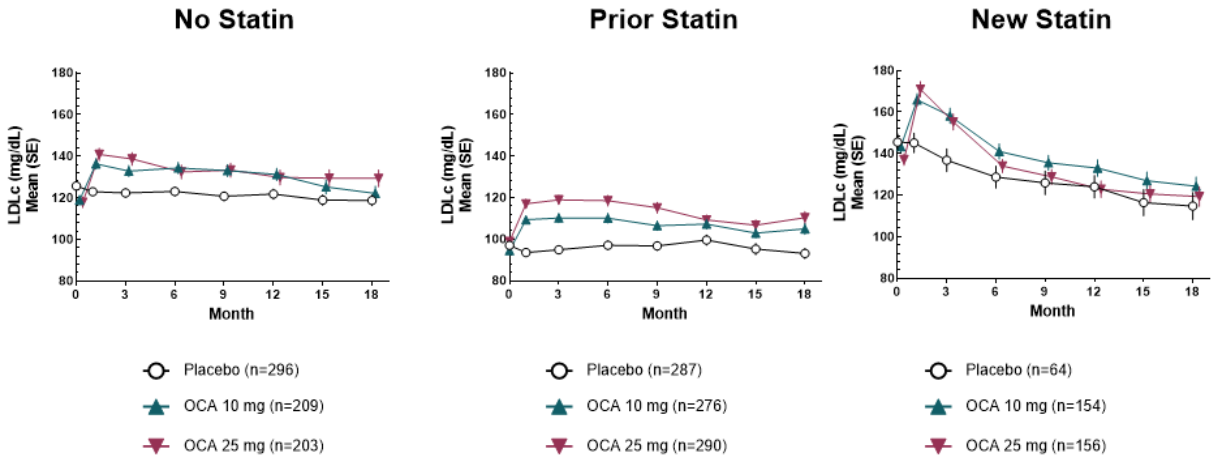
Supplementary Figure S4: Improvement of fibrosis and/or resolution of NASH with no worsening of either. The proportion of patients with improvement of fibrosis and/or resolution of NASH with no worsening of either in the ITT population. NASH resolution defined as hepatocellular ballooning = 0 and lobular inflammation = 0 or 1.



Supplementary Figure S5: Normalisation of elevated transaminase levels. The proportion of patients in the ITT population with elevated ALT (n=546) (Panel A) or AST (n=665) (Panel B) at baseline who achieved transaminase levels ≤ULN. For ALT, ULN was defined as 55U/L; for AST, ULN was defined as 34 U/L.



Supplementary Figure S6: Changes in LDLc over time by statin use. Mean (SE) values of change in LDLc from baseline up to month 18 are shown patients who never used statins, patients who were using statins at baseline, and patients who started using statins during the study for each treatment group in the safety population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).



Supplementary Figure S7: Changes in glucose and HbA1C over time by diabetes status. Mean (SE) values of change in glucose (Panels A and C) and HbA1c (Panels B and D) from baseline up to month 18 are shown based on diabetes status for patients from each treatment group in the safety population (○ placebo, ▲ OCA 10-mg, ▼ OCA 25-mg).