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# ASC41, a selective THRβ agonist significantly reduces liver fat and ALT in biopsy-confirmed MASH patients after 12-week treatment: an interim analysis of a 52-week serial liver biopsy study

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## Introduction

ASC41 is a liver-targeting small molecule agonist. Oral, once-daily ASC41 tablet was developed using proprietary formulation technology. ASC41-A, an active metabolite from ASC41, is highly potent and selective against THRβ. Three phase I or Ib studies in China were completed in healthy or obese subjects with elevated LDL-C>110 mg/dL. A U.S. Phase I study demonstrated no clinically significant drug-drug interactions between ASC41/ASC41-A and most frequently used antidepressants and statins as well as no significant difference in drug exposure between Americans and Chinese at the same dose.

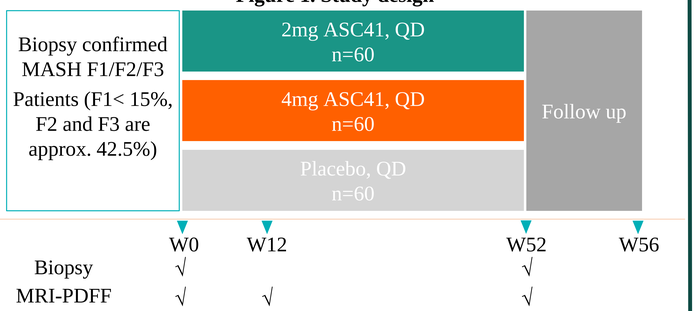
## Aim

The aims are to evaluate the safety, tolerability, and efficacy of ASC41 in adults with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH).

## Method

ASC41-202 (NCT05462353) is a randomized, double-blind, placebo-controlled and multi-center 52-week Phase II clinical study, which enrolls approx. 180 liver biopsy-confirmed Chinese MASH patients. The study design is shown in Figure 1. Primary endpoint is a histological reduction in NAS ≥ 2 points without worsening fibrosis. Secondary endpoints are MASH resolution and fibrosis improvement. Pre-specified interim analysis was conducted when 42 patients completed 12-week treatment. We reported here a pre-specified interim analysis results.

**Figure 1. Study design**




## Results

Baseline characteristics were comparable between ASC41 and resmetirom, except lower BMI and more males for ASC41 (Table 1).
The efficacy results are presented in Table 2.

- Up to 68.2% mean liver fat content (LFC) reduction.
- Up to 93.3% patients achieving at least a 30% relative reduction in LFC.
- Up to 66.7% patients achieving normalized LFC.
- Placebo-adjusted mean reductions in ALT and AST were up to 37.8% and 41.5%.
- Placebo-adjusted mean reductions in LDL-C, TC and TG were up to 27.7%, 23.4% and 46.5%, respectively.

**Table 1. Baseline characteristics**

| Characteristics | ASC41 Phase 2 | | | Resmetirom Phase 2[1] | |
|---|---|---|---|---|---|
| | PBO (n=14) | 2 mg (n=13) | 4mg (n=15) | Placebo (n=41) | 60/80 mg (n=84) |
| Age, years | 41.2(11.6) | 36.1(11.0) | 34.7(6.5) | 47.3 (11.7) | 51.8 (10.4) |
| Male, n(%) | 9(64.3%) | 12(92.3%) | 13(86.7%) | 24 (59%) | 38 (45%) |
| MRI-proton density fat fraction, % fat fraction (SD) | 18.2%(6.7) | 17.8%(5.4) | 18.9%(7.9) | 19.6% (8.2) | 20.2% (6.8) |
| Diabetes, n(%) | 4(28.6%) | 3(23.1%) | 3(20.0%) | 13 (32%) | 36 (43%) |
| Body-mass index, kg/m² | 28.7(3.1) | 29.7(4.8) | 30.4(5.1) | 33.6 (5.8) | 35.8 (6.2) |
| ALT (U/L) | 77.6(56.2) | 65.9(31.2) | 84.8(32.6) | 60.1 (32.2) | 50.0 (29.2) |
| AST (U/L) | 47.9(31.6) | 44.2(23.0) | 53.8(18.2) | 38.0 (20.7) | 35.1 (17.7) |
| HDL-C (mg/dL) | 44.8(8.7) | 58.4(6.0) | 41.5(6.3) | 45.2 (13.4) | 43.8 (12.5) |
| LDL-C (mg/dL) | 116.0(25.4) | 127.5(24.6) | 122.61(25.1) | 116.9 (30.0) | 111.3 (30.4) |
| TG (mg/dL) | 156.8(54.0) | 180.4(74.3) | 228.6(126.5) | 161.1 (75.2) | 178.5 (82.4) |

Data are mean (SD) or n (%) unless otherwise stated.

4 mg ASC41 QD demonstrated a statistically significant CFB of -32.6% in ALT (p=0.0051) and -24.2% in AST (p=0.041) vs placebo at week 12. In contrast, resmetrirom and VK-2809 did not show a statistically significant difference in ALT and AST vs placebo at week 12.[1,2] These data notably differentiate ASC41 from other THRβ agonists.

Safety data is presented in Table 3.

- AEs were similar among the cohorts receiving ASC41 tablet treatment versus the placebo.
- Levels of thyroid axis hormones, including TSH, FT3 and FT4 were relatively unchanged from baseline among the cohorts receiving ASC41 tablet treatment versus the placebo.
- Changes in vital signs and ECG were similar among patients receiving ASC41 tablet treatment versus placebo.

## Conclusions

**Significant reductions in Liver fat, ALT, AST and lipids as well as excellent safety and tolerability profile at week 12 warrant further clinical studies for ASC41 tablet.**

**Table 2. Changes from baseline (CFB) in LFC, liver enzymes and lipids biomarkers at week 12.**

| Parameters | Placebo (n = 14) | ASC41 Tablet | |
|---|---|---|---|
| | | 2 mg, QD (n = 13) | 4 mg, QD (n = 15) |
| Mean relative CFB in LFC | -13.1% | -55.0% (p = 0.0001) | -68.2% (p < 0.0001) |
| Percentage of patients achieving LFC reduction ≥ 30% | 21.4% | 92.3% (p = 0.0002) | 93.3% (p < 0.0001) |
| Percentage of patients achieving LFC reduction ≥ 50% | 21.4% | 46.2% (p = 0.24) | 86.7% (p = 0.0004) |
| Percentage of patients achieving ≤5% absolute LFC | 0.0% | 30.8% (p = 0.16) | 66.7% (p = 0.0017) |
| Mean relative CFB in ALT | 5.2% | -8.5% (p = 0.61) | -32.6% (p = 0.0051) |
| Percentage of patients achieving ALT reduction > 17 U/L | 21.4% | 30.8% (p = 0.68) | 73.3% (p = 0.0052) |
| Mean relative CFB in AST | 17.3% | -3.6% (p = 0.67) | -24.2% (p = 0.041) |
| Mean relative CFB in LDL-C | 4.3% | -19.4% (p = 0.0002) | -23.4% (p < 0.0001) |
| Mean relative CFB in TC | 3.4% | -16.8% (p < 0.0001) | -20.0% (p < 0.0001) |
| Mean relative CFB in TG | 3.9% | -30.6% (p = 0.0001) | -42.6% (p < 0.0001) |

**Table 3. Safety data**

| Event, n(%) | Placebo (n = 14 ) | ASC41 Tablet | |
|---|---|---|---|
| | | 2 mg, QD (n = 13) | 4 mg, QD (n = 15) |
| TEAEs | 13(92.9%) | 13(100%) | 15(100%) |
| Drug-related TEAEs | 6(42.9%) | 7(53.9%) | 7(46.7%) |
| Grade 1 | 6(42.9%) | 7(53.9%) | 7(46.7%) |
| Drug-related GI AEs | 2(14.3%) | 3(23.1%) | 1(6.7%) |
| Nausea | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Vomiting | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Diarrhea | 1(7.1%) | 3(23.1%) | 1(6.7%) |
| Abdominal distension | 1(7.1%) | 0(0.0%) | 0(0.0%) |
| Abdominal pain (upper) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Constipation | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Dyspepsia | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| Frequent bowel movements | 0(0.0%) | 0(0.0%) | 0(0.0%) |

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**Abbreviation:** ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL-C: low-density lipoprotein cholesterol; LFC: liver fat content; TC: total cholesterol; TG: triglyceride; AEs: adverse events; ECG: electrocardiogram; TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine.

**Reference:** [1]. Harrison, S. A., et al.[J] Lancet, (2019).DOI: 10.1016/s0140-6736(19)32517-6; [2]. Viking press release, May 2023