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A Phase Ib Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ASC41, a THR-β Agonist, for 28-days in Overweight and Obese Subjects with Elevated LDL-C, a Population with Characteristics Of NAFLD

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INTRODUCTION

Nonalcoholic fatty liver disease (**NAFLD**), a continuum of liver abnormalities from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (**NASH**)[1], has become a major public health issue worldwide as NASH can lead to cirrhosis and hepatocellular carcinoma. The prevalence of NASH is increasing In both the United States and Asia[2]. Currently there are no approved pharmacological interventions for NASH.

Thyroid hormone receptor beta (**THR-β**) agonists can increase metabolism, reduce elevated lipid parameters, and improve liver histology in patients with NASH steatosis[3]. Thus THR-β agonists have been identified as a promising treatment of NASH. **ASC41** is a potent, hepatic targeting, and selective THR-β agonist small molecule prodrug. ASC41 is converted to its pharmacologically active metabolite ASC41-A by CYP3A4 in the liver. ASC41 has been formulated in commercially ready oral tablets developed in-house using proprietary technology.

Here we present the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of ASC41 oral tablets in overweight and obese subjects. (NCT04686994)

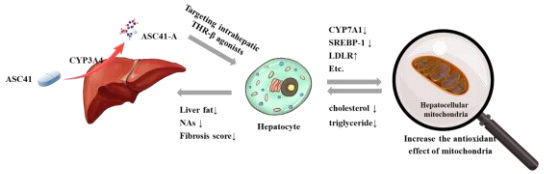

Figure 1: MoA of the THR-β agonist, ASC41, against NAFLD

AIM

To evaluate the safety, tolerability, PK and lipid lowering potential of ASC41 oral tablets in obese or overweight subjects with LDL-C > 110 mg/dL, a population with characteristics of NAFLD.

METHODS

This Phase Ib trial was a single-center, randomized, double-blind, placebo-controlled, parallel-group study. Obese or overweight subjects with LDL-C > 110 mg/dL were randomly assigned (3:1 ratio) to receive ASC41 tablets or placebo tablets at a dose of 10 mg once daily for 28 days.

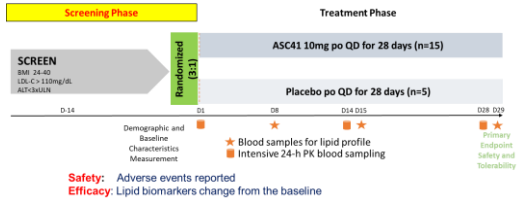

Figure 2: Study design

Intensive PK blood samplings were performed on D1, D14 and D28. The validated LC-MS/MS analysis method was used to determine the plasma concentrations of ASC41 and ASC41-A. Efficacy was determined by change of the blood lipid biomarkers from the baseline, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein B (Apo-B) and lipoprotein(α) (LP(α)).

Ninety-six subjects were screened to randomize 20 (15 males, 5 females) to receive ASC41 and placebo in 3:1 ratio. Seventeen subjects received continuous administration for 28 days, while 13 subjects were qualified for PK evaluation.

Table 1: Demographic and baseline characteristics

Parameter (unit)	ASC41	Placebo
N	15	5
Age(Years), Mean (SD)	31（6）	26（9）
Male, n (%)	12（80.0）	3（60.0）
BMI (kg/m2), Mean (SD)	27（3）	0 27（4）
N	13	4
LDL-C (mmol/L)，Mean (SD)	3.59（0.46）	4.04（0.81）
TC (mmol/L)，Mean (SD)	5.50（0.60）	5.76（1.04）
HDL-C (mmol/L), Mean (SD)	1.37（0.27）	1.26（0.24）
Apo-A (g/L)，Mean (SD)	1.29（0.18）	1.17（0.14）
Apo-B (g/L)，Mean (SD)	0.96（0.12）	1.10（0.19）
LP(a) (g/L)，Mean (SD)	127.49（225.68）	501.74（449.86）

RESULTS

Table 2: Adverse events (AEs)

	ASC41 (N=15)	Placebo (N=5)
Subjects with treatment-related AEs, n(%)	15(100%)	5(100%)
Grade I	15(100%)	5(100%)
Grade II	5(33%)	1(33%)
Grade III	2(13%)	1(33%)
Subjects with drug-related serious AEs (SAEs)	0	0
AEs occurring in ⩾10%, n(%)		
Hyperglycemia	2(13%)	0
hypertriglyceridemia	0	1(20%)
Hyperuricemia	0	1(20%)
urinary tract infection	0	2(40%)
Grade 3 laboratory changes (CTCAE), n(%)		
Elevated ALT	1(6.7%)	0

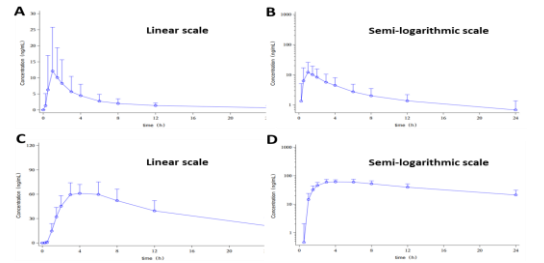

Figure 3: Mean ASC41 (A, B) and ASC41-A (C, D) plasma concentration versus time profiles on Day 1.

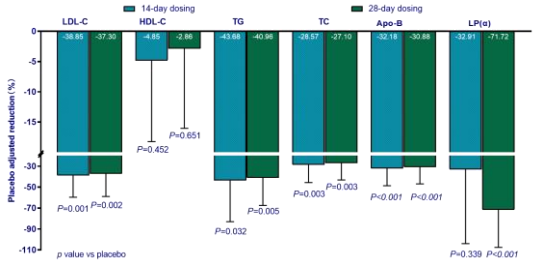

Figure 4: Oral administration of 10 mg ASC41 tablets in overweight and obese subjects for 14 and 28 days resulted in a significant reduction of plasma LDL-C, TG, TC, Apo-B and LP(α).

- The exposure of ASC41 and ASC41A at 10 mg QD showed an approximately linear increase as compared to the dose range between 1-5 mg QD which were tested previously. There was no significant difference in the main PK parameters of both ASC41 and ASC41A between male and female (P > 0.05).
- Most AEs were Grade 1-2. No serious AEs or adverse reactions above Grade 3 were observed during the study.
- Compared with placebo, lipid parameters (LDL-C, TG, TC, Apo-B, and LP (α)) in subjects treated with ASC41 for 28 consecutive days showed clinically meaningful and statistically significant reductions (P<0.05).

CONCLUSION

Results of this study showed that oral administration of ASC41 was safe and well-tolerated, and ASC41 treatment for consecutive 28 days resulted in a significant reduction of LDL-C, TG, TC, Apo-B, and LP (α) in obese or overweight subjects. Our findings support advancement of the ASC41 clinical program for the indication of NASH.

The successful development of commercially-ready oral tablet formulation will accelerate ASC41 clinical development.

REFERENCES

[1] *Nat Med.* 2018;24(7):908-922.
[2] *J Hepatol.* 2021;S0168-8278(21)02086-9.
[3] *Lancet* 2019; 394: 2012–24

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