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ASC41, a thyroid hormone receptor β agonist, showed little drug interaction, significant lipid reduction and comparable pharmacokinetic profiles among Chinese and US healthy subjects and patients with non-alcoholic fatty liver disease (NAFLD): results from two phase 1 studies

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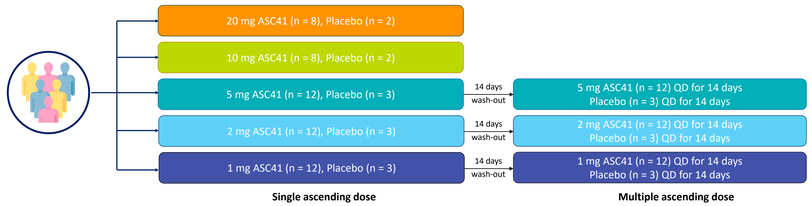
Background

- Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. Non-alcoholic steatohepatitis (NASH), the severe form of NAFLD, may progress to liver cirrhosis and hepatocellular cancer. NASH is also a leading cause of liver transplantation. Although steady progress has been made in understanding disease epidemiology, pathogenesis and identifying therapeutic targets, there is no FDA approved therapy for this disease.
- ASC41 is a small molecule prodrug, which is converted to its pharmacologically active metabolite ASC41-A by CYP3A4 in the liver. ASC41-A is a potent and selective thyroid hormone receptor β (THR-β) agonist. Here we report results of ASC41 drug-drug interaction (DDI) study in US healthy subjects and pharmacokinetics (PK), safety and pharmacodynamics (PD) in Chinese healthy subjects or US subjects with NAFLD.

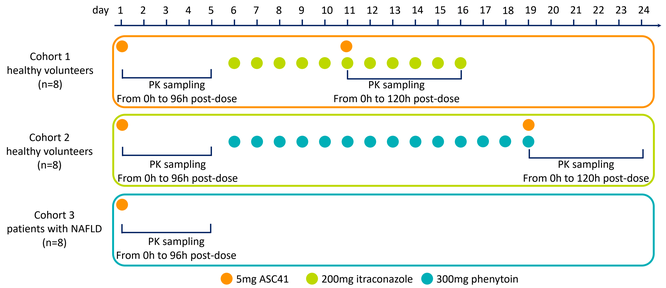
Methods

NCT04527250 was a phase I, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, PK and PD of single and multiple ascending oral doses of ASC41 tablets in Chinese healthy volunteers.



Study design (NCT04527250)

NCT04845646 was a phase I, open label, drug-drug interaction study to evaluate the effect of itraconazole and phenytoin on the pharmacokinetics of ASC41 tablets given orally in US healthy volunteers and to evaluate the PK, safety and tolerability in US patients with NAFLD.



Study design (NCT04845646)

Results

- In the study of Chinese healthy volunteers, the pharmacokinetic parameters (C_{max}, AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, $C_{max,ss}$, $AUC_{0-\tau}$, $AUC_{0-t,ss}$) of ASC41 and ASC41-A in each dose group after single dose and multiple doses of ASC41 tablets were highly correlated with doses, showing a linear PK profile.
- PK profiles of ASC41 and ASC41-A were similar among US and Chinese healthy subjects, as well as NAFLD patients following a single dose of 5 mg ASC41 tablet **(Figure 1).**
- There were no clinically significant changes in the exposure of ASC41-A in the presence or absence of itraconazole (CYP3A4 strong inhibitor) or phenytoin (CYP3A4 strong inducer).
- In the multiple-ascending dose clinical study in healthy subjects with 110mg/dL < low-density lipoprotein cholesterol (LDL-C) < 190mg/ dL, after 14 days of once daily oral administration of ASC41 tablets, the triglyceride (TG) of 1 mg, 2 mg and 5 mg groups and LDL-C of 5 mg group showed clinically and statistically significant decrease compared with the placebo group ($P<0.05$) **(Table 1).**
- No serious adverse events were reported across studies, and most adverse events were mild (grade 1) in severity and all were resolved with no sequelae.

Conclusions:

- **PK of ASC41 and ASC41-A was comparable among US and Chinese healthy subjects and NAFLD patients.**
- **ASC41 demonstrated significant reductions of lipids.**
- **ASC41 exhibited satisfactory safety and tolerability.**
- **Drug-Drug interactions of ASC41/ASC41-A with strong CYP3A4 inhibitor or inducer were low. It is unlikely that there will be clinically significant drug-drug interactions between ASC41/ASC41-A and the most frequently used antidepressants and statins, indicating broad application in patients with NASH.**
- **ASC41 tablet is currently in a 52-week Phase 2 trial to treat biopsy-confirmed NASH patients.**

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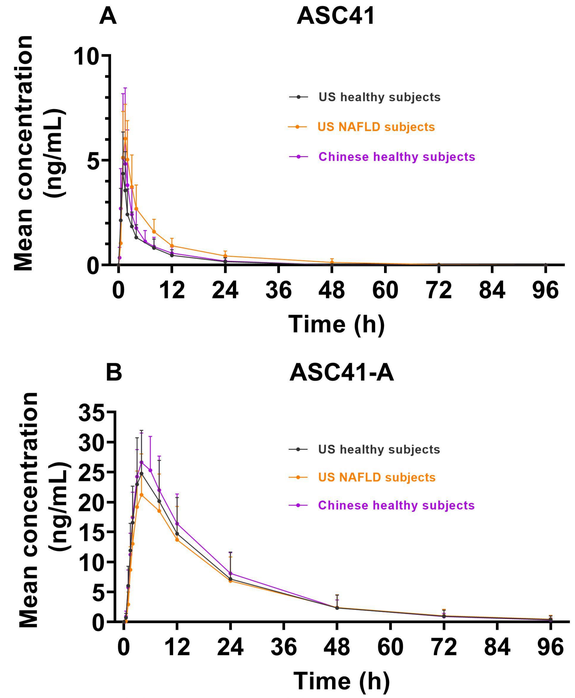

Figure 1. Mean ASC41 (A) and ASC41-A (B) plasma concentration versus time profiles following a single oral dose of 5 mg ASC41 in US healthy and NAFLD subjects and in Chinese healthy subjects

	1 mg (n=12)	2 mg (n=12)	5 mg (n=12)
Placebo-adjusted LDL-C reduction	-0.42%	-11.94%	-19.99%
P-value vs placebo	p=0.947	p=0.052	p=0.002
Placebo-adjusted triglyceride reduction	-39.43%	-31.06%	-34.49%
P-value vs placebo	p=0.002	p=0.029	p=0.015
Placebo-adjusted TC reduction	-1.48%	-8.53%	-10.71%
P-value vs placebo	p=0.766	p=0.142	p=0.030
Placebo-adjusted HDL-C reduction	8.11%	-2.54%	-0.22%
P-value vs placebo	p=0.135	p=0.668	p=0.962

Table 1. Placebo-adjusted relative change (mean) from baseline after 14 days of once daily oral dosing of ASC41 tablets