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ASC42, a Novel Non-steroidal FXR Agonist, Demonstrates a Normal Cholesterol Profile and Lack of Pruritus at Therapeutic Doses in a 14-day Phase I Randomized, Double-blind, Placebo Controlled Study in Healthy Volunteers

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INTRODUCTION

Nonalcoholic fatty liver disease (**NAFLD**) is a condition in which fat builds up in the liver. Nonalcoholic steatohepatitis (**NASH**), the more severe form of NAFLD, is associated with inflammation and hepatocyte damage, and can lead to cirrhosis and hepatocellular carcinoma. The prevalence of NASH is alarmingly growing. Currently there is no approved treatment for NASH.

Farnesoid X receptor (**FXR**) agonists can reduce steatosis, inflammation, and improve fibrosis, and are the most advanced class of drugs in development for the treatment of NASH. **ASC42** is a potent, orally available, non-steroidal FXR agonist.

Here we present the results of safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD), from a first-in-human (FIH) study following single- and multiple-ascending doses (SAD and MAD) and food effect in healthy volunteers (HVs). (NCT04679129)

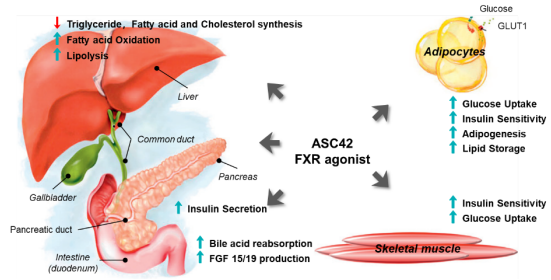

Figure 1: MoA of the FXR agonist, ASC42, against NASH

AIM

To evaluate the safety and tolerability of ASC42.

To establish Phase II human therapeutic doses of ASC42 based on PD biomarkers of 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19).

To investigate food effect on ASC42 exposure.

METHODS

This was a 2-part, Phase 1, FIH, double-blind, placebo-controlled study, consisting of 8 cohorts of 8 subjects each (6 active: 2 placebo), divided as follows:

Part Ia: SAD study including Cohorts 1 to 5 with proposed dose levels of 5, 15, 50, 100, and 200 mg, respectively.

Part Ib: A crossover design of Cohort 2 (15 mg) to study the food effect on the PK of ASC42.

Part II: MAD study including Cohorts 6 to 8 with proposed dose levels of 5, 15, and 50 mg, respectively.

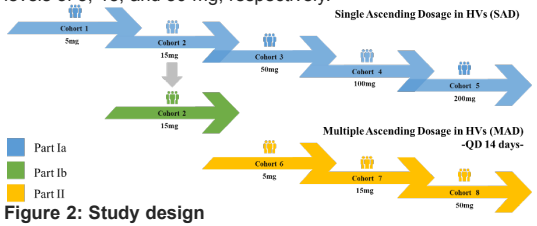

Figure 2: Study design

HIGHLIGHTS

- Both animal models and human PD biomarkers data suggest that **15 mg QD is one of the human therapeutic doses of ASC42**.
- No pruritus observed during ASC42 15 mg QD treatment for 14 days .
- ASC42 15 mg QD treatment for consecutive 14 days showed a significant increase of FGF19 level (1780% of baseline) and suppression of C4 level to a reduction of 91%.
- Mean LDL-C and HDL-C values remained within normal limits and there were no treatment-emergent ALT and AST elevations with 5 mg, 15 mg and 50 mg QD of ASC42 for 14 days.
- ASC42 was safe and generally well tolerated when administered as single doses up to 200 mg and multiple daily doses for 14 days up to 50 mg.
- AUC at 5, 15 and 50 mg on day 14 was 196, 1752 and 10970 ng.h/mL, respectively, indicating the exposure changed in an over-dose proportional manner with minimal food effect.

RESULTS

Table 1: TEAEs and SAEs

	Part I (SAD)						Part II (MAD)			
n (%)	Cohort 1 ASC42 5 mg (N = 6)	Cohort 2 ASC42 15 mg (N = 6)	Cohort 3 ASC42 50 mg (N = 6)	Cohort 4 ASC42 100 mg (N = 6)	Cohort 5 ASC42 200 mg (N = 6)	Pooled Placebo (N = 10)	Cohort 6 ASC42 5 mg (N = 6)	Cohort 7 ASC42 15 mg (N = 6)	Cohort 8 ASC42 50 mg (N = 7)	Pooled Placebo (N = 6)
Any TEAE	1 (16.7)	2 (33.3)	0	0	3 (50.0)	1 (10.0)	1 (16.7)	0	6 (85.7)	2 (33.3)
mild	1 (16.7)	2 (33.3)	0	0	2 (33.3)	1 (10.0)	0	0	2 (28.6)	2 (33.3)
moderate	1 (16.7)	0	0	0	1 (16.7)	0	1 (16.7)	0	3 (42.9)	0
severe	0	0	0	0	0	0	0	0	2 (28.6)	0
life threatening	0	0	0	0	0	0	0	0	0	0
fatal	0	0	0	0	0	0	0	0	0	0
Any SAE	0	0	0	0	0	0	0	0	1 (14.3)	0
Any TEAE related to study drug	0	0	0	0	0	0	0	0	4 (57.1)	1 (16.7)
Any TEAE leading to withdrawal	0	0	0	0	0	0	0	0	1 (14.3)	0
Any TEAE leading to death	0	0	0	0	0	0	0	0	0	0

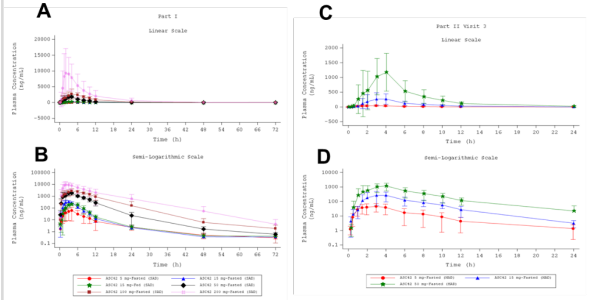

Figure 3: Mean (±SD) ASC42 plasma concentration versus time for Part I SAD as shown in A (linear) and B (semi-logarithmic), and for Part II MAD as shown in C (linear) and D (semi-logarithmic).

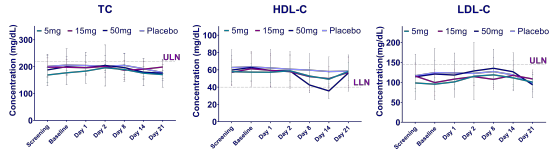

Figure 4: Total Cholesterol (TC), HDL-C and LDL-C remained within normal limits during 14 days ASC42 treatment.

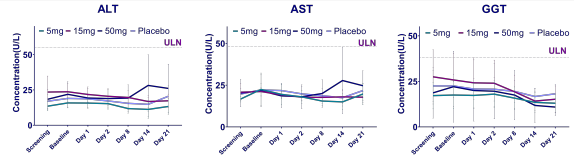

Figure 5: No treatment-emergent ALT, AST and GGT elevations during 14 days ASC42 treatment at therapeutic dose.

CONCLUSION

Results of this study indicated that 15 mg QD is one of the human therapeutic doses of ASC42 and no pruritus was observed during 14 days treatment at this therapeutic dose. Although pruritus was observed during 14 days treatment with 50 mg QD ASC42, there is **a 6.3-fold safety margin between 15 mg and 50 mg** (Table 2). There were no elevated ALT/AST or lipid parameter abnormalities during 14 days treatment up to 50 mg QD.

Based on these data, 15 mg QD has been selected as one of three treating doses to be studied in the ASC42 Phase II trial in patients with NASH.

Table 2: Study summary

Dose	5 mg QD	15 mg QD	50 mg QD
Incidence rate of pruritus during 14 days treatment (%)	0	0	57
AUC on Day 14 (ng.h/mL)	196	1752	10970
Safety margin for pruritus versus 50 mg (fold)	56	6.3	NA
LDL-C change from baseline on Day 14 (%, Median)	-6.6	2.43	-14.8
FGF19 on Day 14 versus baseline (%)	471	1780	3970
C4 reduction on Day 14 (%)	53	91	96
ALT change from baseline on Day 14 (U/L, Median)	-1.0	-2.5	3

CONTACT INFORMATION

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