Significant lipid lowering by ASC41, an oral tablet, liver-targeted THRβ agonist, in a phase I randomized, double-blind, placebo controlled single- and multiple-ascending dose study

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INTRODUCTION

- Non-alcoholic fatty liver disease (NAFLD) is one the fastest emerging manifestations of the metabolic syndrome worldwide. Non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD, may progress to cirrhosis and its' complications including hepatocellular cancer and is presently a leading cause of liver transplantation. Although steady progress has been made in understanding disease epidemiology, pathogenesis and identifying therapeutic targets, the slowest advancement is seen in therapeutic success. Currently, there is no FDA approved pharmacotherapy for this disease and effective therapeutic targets are urgently warranted.
- ASC41 is a small molecule, hepatic targeting, potent and selective thyroid hormone receptor beta (THR-β) agonist prodrug, which is converted to its pharmacologically active metabolite ASC41-A by CYP3A4 in the liver. It has been formulated in commercially ready oral tablets developed in-house using proprietary technology.

AIM

- To evaluate the safety, tolerability, pharmacokinetics and lipid lowering potential of ASC41 oral tablets in subjects with low density lipoprotein cholesterol (LDL-C) > 110 mg/dL

METHOD

- This was a phase I, randomized, double-blind, placebo (PBO) controlled single- and multiple-ascending dose study in 65 subjects with elevated LDL-C (> 110 mg/dL).
- In the single-ascending dose (SAD) portion of the study, subjects were treated with 1 mg (n=15), 2 mg (n=15), 5 mg (n=15), 10 mg (n=10) or 20 mg (n=10) ASC41 oral tablets or matching PBO tablets.
- In the multiple-ascending dose (MAD) portion of the study, subjects were treated with 1 mg (n=15), 2 mg (n=15) or 5 mg (n=15) ASC41 oral tablets or matching PBO tablets, QD for 14 days.
- A washout period of at least 14 days was required between the SAD and MAD portions of this study.

RESULTS

- ASC41 and ASC41-A showed dose-proportional pharmacokinetic profiles from 1 mg to 20 mg (SAD).
- ASC41 and ASC41-A displayed dose-proportional pharmacokinetic profiles from 1 mg to 5 mg following 14-day QD dosing (MAD).
- There was a high correlation between major pharmacokinetic parameters and dose in SAD and MAD, demonstrating linear PK characteristics.
- In the MAD portion, data showed that after 14 days of oral QD dosing, subjects demonstrated clinically meaningful and statistically significant reductions in LDL-C and triglycerides compared to PBO , with no significant impact on HDL-C (table 2).
- ASC41 was tolerable and had a benign adverse event (AE) profile at all doses following 14-day treatment. There were no grade 3 AEs, serious adverse events or premature discontinuations.

Table 2. Placebo-adjusted relative change (mean) from baseline after 14 days of once daily oral dosing of ASC41 tablets

	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: Dosage and Administration:

Group (N=65)		Dosage Regimen	
		Single-ascending Dose (SAD)	Multiple-ascending Dose (MAD) *
Group 1 (1 mg)	IP (n=12)	IP/PBO, 1 mg, po fasting, 1 tablet.	IP/PBO, 1 mg, po fasting, 1 tablet, QD, ×14 days.
	PBO (n=3)		
Group 2 (2 mg)	IP (n=12)	IP/PBO, 1 mg, po fasting, 2 tablets.	IP/PBO, 1 mg, po fasting, 2 tablets, QD, ×14 days.
	PBO (n=3)		
Group 3 (5 mg)	IP (n=12)	IP/PBO, 5 mg, po fasting, 1 tablet.	IP/PBO, 5 mg, po fasting, 1 tablet, QD, ×14 days.
	PBO (n=3)		
Group 4 (10 mg)	IP (n=8)	IP/PBO, 5 mg, po fasting, 2 tablets.	—
	PBO (n=2)		
Group 5 (20 mg)	IP (n=8)	IP/PBO, 5 mg, po fasting, 4 tablets.	—
	PBO (n=2)		

***** The washout period is at least 14 days, followed by multiple-dose stage. **IP:** investigational drug (ASC 41 table). **PBO:** placebo

CONCLUSIONS

- These data 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.

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