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A Phase I, single-dose study to evaluate the safety, tolerability, and pharmacokinetics of ASC43F, a fixed-dose combination oral tablet of ASC41, a thyroid hormone receptor Beta agonist, and ASC42, a farnesoid X receptor agonist in healthy subjects

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Background and Aim

Non-alcoholic fatty liver disease (NAFLD) is a condition where excess fat accumulates in the liver and NASH (non-alcoholic steatohepatitis) is defined as a more serious form of NAFLD, associated with inflammation and hepatocyte damage. The complexities of NASH biology coupled with the numerous failures of monotherapy suggest that one therapeutic target may be insufficient to improve the histologic findings in NASH. Thus, targeting more than one pathway that causes and/or accelerates disease progression may improve efficacy.

Both thyroid hormone receptor beta (**THR-β**) and farnesoid X receptor (**FXR**) agonists have shown some success in improving different and complementary aspects of NASH histology

ASC41 is an oral hepatic targeting THR-β agonist prodrug. The active metabolite (ASC41-A) of ASC41 is a selective THR-β agonist. Three Phase I and Ib clinical trials of ASC41 have been completed and results indicated that subjects demonstrated a clinically meaningful and statistically significant reduction of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) after 14 or 28 days of ASC41 treatment compared to placebo.

ASC42 is a novel non-steroidal, selective, potent, oral FXR agonist with best-in-class potential. The Phase I clinical data indicated that FXR target engagement biomarkers FGF19 increased 1680% and C4 decreased 91% after ASC42 15mg QD treatment for 14 days. At this therapeutic dose of 15mg QD, there was no pruritus and mean LDL-C value remained within normal limit.

ASC43F is a fixed-dose combination (FDC) tablet of ASC41 and ASC42 with three dosage strengths (ASC41/ASC42: 2mg/10mg, 4mg/15mg and 5mg/15mg). This study aimed to evaluate the safety, tolerability, and pharmacokinetics (PK) of ASC43F in healthy volunteers.

Methods

Study Design

ASC43F-101 (NCT05118516) is an open-label, single-dose, phase I study in healthy volunteers. Eight subjects aged 18 to 65 years who weighed at least 50 kg for men, and at least 45 kg for women and had body mass index (BMI) within the range of 18.5-32 kilogram per meter square (kg/m^2) were planned to be enrolled in this study. Two eligible subjects would be enrolled first. After the 7-day safety assessment of the first two sentinel subjects and no stopping rule was met, the remaining 6 subjects would be enrolled.

Study Procedure

Following screening procedures and baseline (Day 0) assessments, eligible subjects would be enrolled and receive a single tablet of ASC43F (ASC41 5 mg and ASC42 15 mg) by mouth with 240 ml water on Day 1. PK blood samples would be collected at predose (0 hours) and 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72 hours post dose. Once all Day 4 assessments were completed, subjects would be discharged from the study site. On Day 7, subjects would return to the study site for safety evaluations.

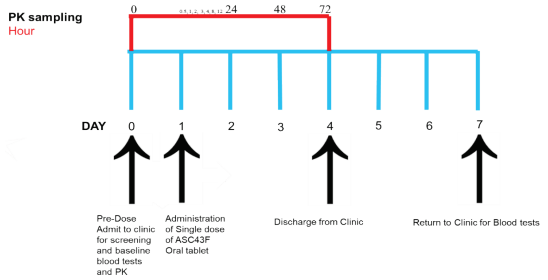

Figure 1: Study Dosing Scheme

Results

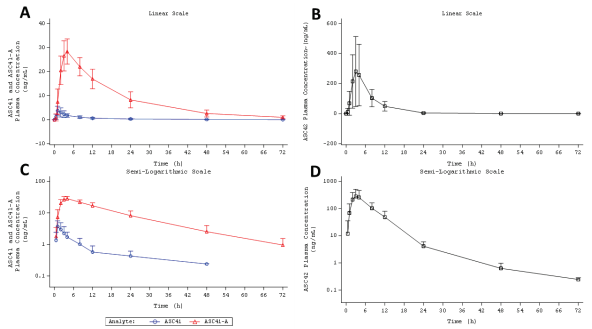

Figure 2: Mean (±SD) plasma concentration of ASC41/ASC41-A and ASC42 from ASC43F versus time shown in A, B (linear) and C, D (semi-logarithmic).

Table 1: Summary of PK parameters

Parameter (unit)	Statistic	ASC41 (N = 8)	ASC41-A (N = 8)	ASC42 (N = 8)
C_{max} (ng/mL)	n	8	8	8
	Mean (SD)	4.01 (1.96)	28.9 (5.57)	312 (200)
	GM	3.60	28.4	254
	GeoCV%	53.7	20.3	84.2
T_{max} (h)	n	8	8	8
	Median	1.00	4.00	3.00
	(min, max)	1.00, 2.00	3.00, 4.00	3.00, 8.00
AUC_{last} (ng*h/mL)	n	8	8	8
	Mean (SD)	24.4 (15.3)	543 (148)	1869 (1089)
	GM	20.8	527	1580
	GeoCV%	65.4	26.7	72.4
AUC_{0-24} (ng*h/mL)	n	8	8	8
	Mean (SD)	22.5 (10.9)	389 (77.2)	1820 (1071)
	GM	20.5	382	1532
	GeoCV%	48.9	20.0	73.5
AUC_{inf} (ng*h/mL)	n	8	8	8
	Mean (SD)	27.8 (17.1)	565 (162)	1873 (1089)
	GM	23.8	546	1584
	GeoCV%	64.9	28.2	72.3
$t_{1/2}$ (h)	n	8	8	8
	Mean (SD)	8.76 (5.53)	14.8 (2.13)	8.27 (2.80)
	GM	7.28	14.7	7.84
	GeoCV%	74.3	14.2	36.9
V_z/F (L)	n	8	NC	8
	Mean (SD)	2249 (485)	NC	126 (76.2)
	GM	2205	NC	107
	GeoCV%	21.2	NC	66.1
CL/F (L/h)	n	8	NC	8
	Mean (SD)	242 (128)	NC	11.5 (8.11)
	GM	210	NC	9.47
	GeoCV%	64.9	NC	72.3

Table 2: Summary of PK parameters of ASC41, ASC41-A, and ASC42 from ASC43F versus monotherapy in healthy volunteers

	ASC42 Tablet (5mg*3)	ASC41 Tablet (5mg*1)		ASC43F Tablet (ASC41 5mg + ASC42 15mg)		
	ASC42	ASC41	ASC41-A	ASC42	ASC41	ASC41-A
C_{max} (ng/mL)	363 (29.5)	4.69 (35.2)	23.9 (32.9)	254 (84.2)	3.60 (53.7)	28.4 (20.3)
T_{max} (h)	2.50	1.00	4.00	3.00	1.00	4.00
$t_{1/2}$ (h)	8.11 (22.9)	6.75 (33.2)	15.5 (26.8)	7.84 (36.9)	7.28 (74.3)	14.7 (14.2)
AUC_{0-t} (ng·h/mL)	1631 (27.0)	16.7 (54.9)	442 (52.9)	1580 (72.4)	20.8 (65.4)	527 (26.7)
AUC_{0-inf} (ng·h/mL)	1635 (26.9)	23.8 (37.5)	455 (53.2)	1584 (72.3)	23.8 (64.9)	546 (28.2)

Table 3: Summary of adverse events

AE category	Overall (N=8)	
	No. of subjects (%)	No. of events
Any TEAE	1 (12.5)	1
Mild	1 (12.5)	1
Moderate	0	0
Severe	0	0
Any SAE	0	0
Any study drug-related TEAE	1 (12.5)	0
Any study drug-related SAE	0	0
Investigations	1 (12.5)	1
Alanine aminotransferase increased	1 (12.5)	1

Conclusion

Results of this Phase I study demonstrated that ASC43F showed good tolerability and safety profiles, and PK parameters of ASC41/ASC41A and ASC42 from ASC43F were similar to those of ASC41 and ASC42 as monotherapy. ASC43F is a one-pill, once-a-day FDC for NASH treatment, thus will improve patient compliance.

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