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ASC43F Tablet as a One-pill, Once-a-day Fixed-dose Combination of ASC41, a THR-β Agonist, and ASC42, a FXR Agonist, Demonstrated Comparable Dissolution Profiles and *in vivo* Pharmacokinetics VS. Single ASC41 and ASC42 Tablets

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INTRODUCTION

The complexities of nonalcoholic steatohepatitis (**NASH**) biology coupled with the numerous failures of monotherapy suggest that one therapeutic target may be insufficient to improve the histologic findings in NASH.

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, and are currently in Phase 3 clinical trials.

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 one-pill, once-a-day fixed-dose combination (FDC) of ASC41 and ASC42. Here we report *in vivo* pharmacokinetics (PK) and dissolution profiles of ASC43F tablets, in comparison with those of a single ASC41 or ASC42 tablet.

AIM

This study aimed to investigate the stability of ASC43F and to compare the *in vivo* PK and dissolution profiles of ASC43F tablets with those of a single ASC41 or ASC42 tablet.

METHODS

***In vivo* PK study**:

The *in vivo* PK study was performed in beagle dogs in a crossover study design. Three male beagles were dosed with ASC42 (3x5 mg tablets), ASC41 (1x5 mg tablet) and ASC43F (1 fixed dose tablet consisting of 15 mg ASC42 and 5 mg ASC41) in the first, second and third period, respectively, with a 5-day washout period in between. Blood was collected up to 48 h, and liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to quantitatively determine the plasma concentrations of ASC41, ASC41-A, and ASC42.

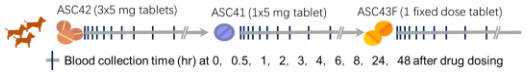

Figure 1: Design of the *in vivo* PK study in beagles

Dissolution study:

Dissolution of ASC43F, ASC41 and ASC42 were performed in 4 different conditions. Dissolution profiles were compared between ASC43F and ASC41 or ASC42.

Stability study:

Accelerated storage stability study of ASC43F was conducted under a temperature of 40 ± 2 °C, RH 75 ± 5%.

HIGHLIGHTS

- The PK parameters of ASC42 and ASC41A in ASC43F tablets remained approximately unchanged as compared to those of a single ASC41 or ASC42 tablet.
- The dissolution profiles of ASC41/ASC42 in ASC43F tablets were similar to those of the single ASC41 or ASC42 tablet using 4 different pH dissolution media.
- The stability data also demonstrated that ASC43F tablets were stable in the accelerated condition of 40℃/75%RH for 4.5 months (equivalent to 1.5 years in the normal condition).

RESULTS

Table1: PK of ASC41/ASC41-A and ASC42 in beagles after an oral dose of 5 mg ASC41, 15 mg ASC42 and ASC43F tablets.

Administration #	#1 Period	#2 Period		#3 Period		
Product	ASC42 Tablet	ASC41Tablet		ASC43F Tablet		
PK Parameters	5 mg*3 Tablet	5 mg*1 Tablet		1 Tablet (ASC41 5 mg+ASC42 15 mg)		
	ASC42	ASC41	ASC41-A	ASC42	ASC41	ASC41-A
C_{max} (ng/mL)	1026	1.74	17.8	1083	2.50	15.63
T_{max} (h)	2.000	0.833	2.000	2.000	2.000	2.667
K_{el} (/h)	0.0746	0.4009	0.1598	0.0803	0.3221	0.1853
$t_{1/2}$ (h)	9.270	1.804	4.764	8.656	2.166	4.066
AUC_{0-t} (ng·h/mL)	4731	4.338	149.2	5674	9.441	129.1
AUC_{0-inf} (ng·h/mL)	4811	4.769	150.7	5755	10.43	129.8

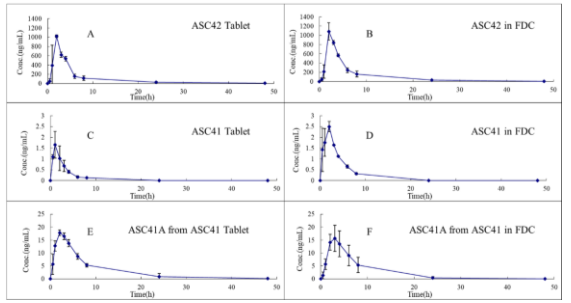

Figure 2: Mean plasma concentration – time profiles of ASC43F (FDC) VS single ASC41 and ASC42 tablets in beagles.

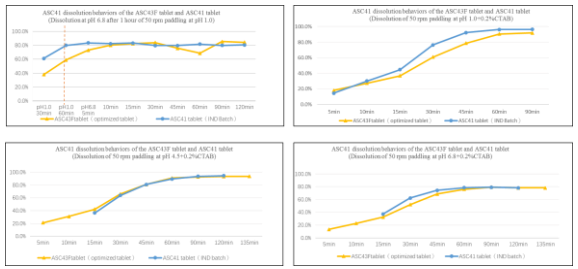

Figure 3: ASC43F (FDC) exhibited similar dissolution profiles as single ASC41 Tablet.

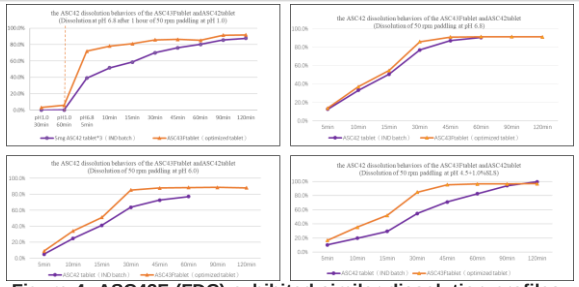

Figure 4: ASC43F (FDC) exhibited similar dissolution profiles as single ASC42 Tablet.

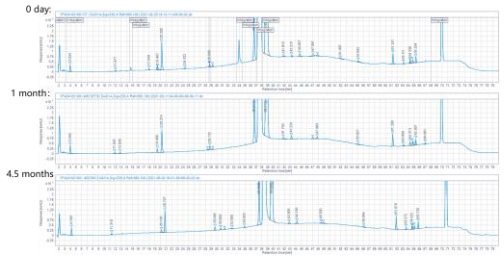

Figure 5: Stability study of ASC43F tablets in the accelerated condition of 40℃/75%RH.

CONCLUSION

Results of this study showed that ASC43F tablets demonstrated comparable *in vivo* PK and dissolution profiles as a single ASC41 or ASC42 tablet. ASC43F is a one-pill, once-a-day FDC for NASH treatment, thus will improve patient compliance.

CONTACT INFORMATION

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