EASL CONGRESS 2023
Vienna, Austria
21–24 June

A phase 2 study of ASC42, a novel farnesoid X receptor (FXR) agonist, in combination with PEGylated interferon (PEG-IFN) and entecavir (ETV) in chronic hepatitis B patients with 12-week treatment

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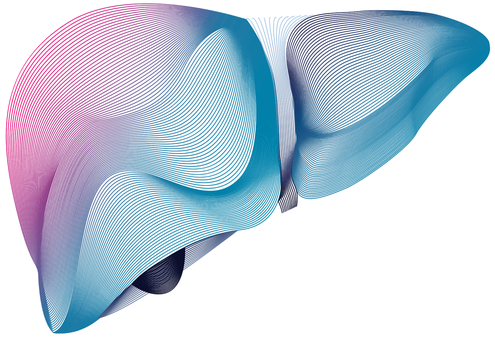
Key Take-home Message:

- In CHB patients, 12-week treatment of 10 mg ASC42 in combination of PEG-IFN-α-2a and ETV was safe and well-tolerated and showed minimum and mild pruritus (6.7%).
- Previous study indicated that in healthy subjects, 14-days treatment of ASC42 alone demonstrated 471-1780% FGF19 increase and 53-91% C4 decrease at a dose range of 5-15 mg.
- Data suggest that at the therapeutic dose of 10 mg, novel FXR agonist ASC42 is differentiated from other FXR agonists in terms of pruritus.



1 Introduction

ASC42 is a novel non-steroidal, selective, potent farnesoid X receptor (FXR) agonist. Preclinical studies showed that ASC42 might be a novel anti-viral candidate for hepatitis B virus (HBV) functional cure through inhibiting transcription of HBV covalently closed circular DNA (cccDNA) into HBV RNA and reducing the HBV cccDNA stability[1]. PEGylated interferon (PEG-IFN) and nucleos(t)ide analogs, such as entecavir (ETV), are the major antiviral drugs for chronic hepatitis B (CHB). As ASC42, PEG-IFN and ETV have different mechanisms of action (MoA), a combination of these 3 drugs might enhance the function cure rates in CHB patients.

2 Aim

This study aimed to evaluate the safety and efficacy of combined treatment of ASC42, PEGylatd interferon-α-2a (PEG-IFN-α-2a) and ETV, and pharmacokinetic (PK) of ASC42 in CHB patients.

3 Method

This Phase 2 trial (NCT05107778) was a multi-center, randomized, single-blind, placebo-controlled study conducted in China. Forty-five HBeAg negative, CHB patients on ETV were randomized equally into 3 cohorts of 10 mg ASC42, 15 mg ASC42 and placebo (PBO) orally once daily (QD) in combination with ETV (0.5 mg, orally QD) and PEG-IFN-α-2a (180 μg, subcutaneous injection once a week). Patients were treated for 12 weeks, and followed for 24 weeks (still on ETV). Serum hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) pregenomic RNA (pgRNA) changes from baseline were measured during the 12-week intervention period and 24-week follow-up period.

4 Results

- 43 CHB patients were enrolled into 10 mg ASC42 (n = 15), 15 mg ASC42 (n = 14) and placebo (n = 14) cohorts. Two subjects in 15 mg ASC42 cohort withdrew from the study due to grade 2 adverse events (AEs) of dermatitis allergic and pruritus, respectively, while the other patients completed the study.

Table 1. Demographic and baseline characteristics of all patients

Characteristic	10 mg ASC42 (N = 15)	15 mg ASC42 (N = 14)	Placebo (N = 14)
Male, n (%)	14 (93.3%)	10 (71.4%)	11 (78.6%)
Age (years), Median (Q1, Q3)	41 (37, 48)	37 (33, 46)	40 (35, 45)
BMI (kg/m^2), Mean (SD)	25.34 (2.449)	24.23 (2.864)	22.92 (2.373)
ALT (U/L), Mean (SD)	26.14 (11.074)	24.22 (11.518)	23.57 (10.704)
HBsAg (log_{10}IU/mL), Mean (SD)	2.94 (0.28)	3.00 (0.32)	2.86 (0.25)

- In total, 122, 119, and 107 AEs were reported in 10 mg, 15 mg ASC42 and PBO cohorts, respectively, and most AEs (94.3%) were mild (grade 1) or moderate (grade 2) in severity. One subject in 15 mg ASC42 cohort experienced a grade 3 serious AE (SAE) of liver function injury with a final outcome of recovered.

Table 2. Summary of all treatment emergent adverse events (TEAEs)

TEAE	10 mg ASC42 (N = 15)		15 mg ASC42 (N = 14)		Placebo (N = 14)	
	Number of cases	Number of patients (%)	Number of cases	Number of patients (%)	Number of cases	Number of patients (%)
Total AEs	122	15 (100.0)	119	14 (100.0)	107	14 (100.0)
Grade ≥ 3 AEs	9	6 (40.0)	7	4 (28.6)	4	3 (21.4))
SAEs	0	0 (0.0)	1	1 (7.1)	0	0 (0.0)
Study drug-related AEs	60	12 (80)	54	12 (85.7)	2	1 (7.1)
Grade ≥ 3 AEs	6	3 (20.0)	3	2 (14.3)	0	0 (0.0)
SAEs	0	0 (0.0)	1	1 (7.1)	0	0 (0.0)
leading to withdraw	0	0 (0.0)	3	2 (14.3)	0	0 (0.0)

- Pruritus is the most common AE, and study drug-related pruritus was reported in 1 (6.7%), 7 (50%) and 0 (0%) subjects in 10 mg, 15 mg ASC42 and PBO cohorts, respectively. Pruritus rate of 10 mg ASC42 (6.7%) is lower than other FXR agonists in NASH patients.

Table 3. Comparison of incidences of pruritus of ASC42 with other FXR agonists and PEG-IFN α-2a

	ASC42 10 mg (N = 15)	Obeticholic Acid 10 mg (N = 653)	PEG-IFN α-2a 180 μg (N = 271)	Cilofexor 30 mg (N = 40)	Tropifexor 140 μg (N = 50)
Patient type	CHB	NASH	CHB	NASH	NASH
Treatment duration	12 weeks	18 months	48 weeks	48 weeks	48 weeks
Pruritus, number of patients (%)	1(6.7)	183 (28)	26 (10)	8 (20)	20 (40)

- ASC42 exposure measures (C_{max} and AUC_{0-24}) in 10 mg cohort is approximately one-third of those in 15 mg cohort (C_{max}: 143 versus 470 [ng/mL]; AUC_{0-2}: 1259 versus 4123 [h*ng/mL]). There was no accumulation following multiple doses.

Table 4. Pharmacokinetic parameters of ASC42

Mean	10 mg ASC42 (N=15)	15 mg ASC42 (N = 14)
AUC_{0-24} (h*ng/mL)	1259.636	4123.2374
$AUC_{0-\infty}$ (h*ng/mL)	1162.9714	6930.149
C_{max} (ng/mL)	143.2467	470.0714
T_{max} (h)	4.4033	5.4452
$t_{1/2}$ (h)	4.0408	14.8895

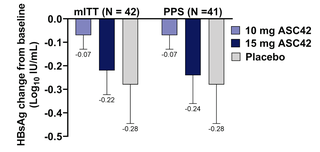


Figure 1. HBsAg changes at Week 12

- No significant changes of HBV specific biomarkers (such as HBsAg) from baseline at end of intervention (Week 12) or follow-up (Week 36)were observed among these 3 cohorts.
- Previous study in healthy subjects showed that ASC42 treatment alone for 14 days induced reduction of pharamcodynamic biomarker, 7α-hydroxy-4-cholesten-3-one (C4) by 53% -91% and increases of fibroblast growth factor 19 (FGF19) by 471% -1780% at a dose range of 5-15 mg, while obeticholic acid could reduce C4 by 71%-79% and increase FGF19 by 97%-236% at a dose range of 10-50 mg in patients with primary biliary cholangitis (PBC).

5 Conclusions

As a novel FXR agonist, 10 mg ASC42 in combination of PEG-IFN-α-2a and ETV, was safe and well-tolerated and showed minimum and mild pruritus (6.7%) in Chinese CHB patients and better pharamcodynamic biomarker 7α-hydroxy-4-cholesten-3-one (C4) inhibition than obeticholic acid.

6 References

Wu J.J, et al. "Significant in vitro and in vivo inhibition of HBsAg and HBV pgRNA with ASC42, a novel non-steroidal FXR agonist." (EASL 2021, abstract PO-1917).

7 Contact information

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