Abstract identifier: SAT-198

ASC41, a selective THRβ agonist significantly reduces liver fat and ALT in biopsy-confirmed MASH patients after 12-week treatment: an interim analysis of a 52-week serial liver biopsy study

Contact information
https://www.gannexpharma.com/
bd@ascletis.com; ir@ascletis.com

Jiangao Fan[1], Junping Shi[2], Hong Wang[3], Minghua Zheng4, Jinjun Chen[5], Yao Xie[6], Fangfang Lv[7], Sikui Wang[8], Ling Yang[9], Qing Xie[10], Yueqiu Gao[11], Chuanwu Zhu[12], Xuebing Yan[13], Qiya Huang[14], Bin Xu[15], Fei Liu[16], Honglian Bai[17], Hong Deng[18], Airong Hu[19], Xin Gao[20], Guoxin Hu[21], Hong You[22], Hong Tang[23], Min Zhang[24], Xiaoling Chi[25], Qin Du[26], Xiaoping Wu[27], Hongzhou Lu[28], Yuguo Zhang[29], Guizhou Zou[30], Huanwei Zheng[31], Yujuan Guan[32], Yue Chen[33], Hua Ye[34], Tianhuang Liu[35], Yuemei Yan[36], Jinzi J. Wu[36]

EASL CONGRESS Milan, Italy 5–8 June 2024

GANNEX
A Member of the Ascletis Group

Introduction

ASC41 is a liver-targeting small molecule agonist. Oral, once-daily ASC41 tablet was developed using proprietary formulation technology. ASC41-A, an active metabolite from ASC41, is highly potent and selective against THRβ. Three phase I or Ib studies in China were completed in healthy or obese subjects with elevated LDL-C>110 mg/dL. A U.S. Phase I study demonstrated no clinically significant drug-drug interactions between ASC41/ASC41-A and most frequently used antidepressants and statins as well as no significant difference in drug exposure between Americans and Chinese at the same dose.

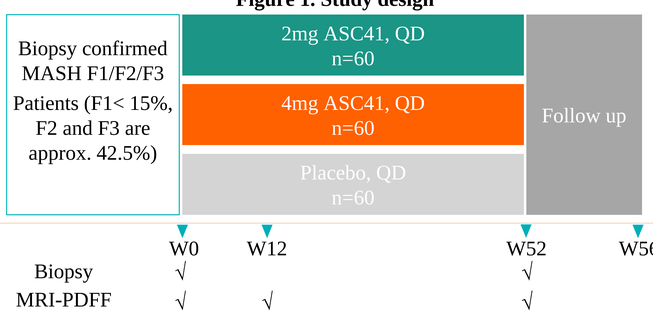
Aim

The aims are to evaluate the safety, tolerability, and efficacy of ASC41 in adults with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH).

Method

ASC41-202 (NCT05462353) is a randomized, double-blind, placebo-controlled and multi-center 52-week Phase II clinical study, which enrolls approx. 180 liver biopsy-confirmed Chinese MASH patients. The study design is shown in Figure 1. Primary endpoint is a histological reduction in NAS ≥ 2 points without worsening fibrosis. Secondary endpoints are MASH resolution and fibrosis improvement. Pre-specified interim analysis was conducted when 42 patients completed 12-week treatment. We reported here a pre-specified interim analysis results.

Figure 1. Study design



Results

Baseline characteristics were comparable between ASC41 and resmetirom, except lower BMI and more males for ASC41 (Table 1).
The efficacy results are presented in Table 2.

- Up to 68.2% mean liver fat content (LFC) reduction.
- Up to 93.3% patients achieving at least a 30% relative reduction in LFC.
- Up to 66.7% patients achieving normalized LFC.
- Placebo-adjusted mean reductions in ALT and AST were up to 37.8% and 41.5%.
- Placebo-adjusted mean reductions in LDL-C, TC and TG were up to 27.7%, 23.4% and 46.5%, respectively.

Table 1. Baseline characteristics

特征	ASC41 2期			Resmetirom 2期[1]	
	安慰剂 (n=14)	2 毫克 (n=13)	4毫克 (n=15)	安慰剂 (n=41)	60/80 毫克 (n=84)
年龄	41.2(11.6)	36.1(11.0)	34.7(6.5)	47.3 (11.7)	51.8 (10.4)
男性患者人数(%)	9(64.3%)	12(92.3%)	13(86.7%)	24 (59%)	38 (45%)
磁共振质子密度脂肪分数，脂肪分数百分比（标准差）	18.2%(6.7)	17.8%(5.4)	18.9%(7.9)	19.6% (8.2)	20.2% (6.8)
糖尿病患者人数(%)	4(28.6%)	3(23.1%)	3(20.0%)	13 (32%)	36 (43%)
身体质量指数, kg/m²	28.7(3.1)	29.7(4.8)	30.4(5.1)	33.6 (5.8)	35.8 (6.2)
ALT (U/L)	77.6(56.2)	65.9(31.2)	84.8(32.6)	60.1 (32.2)	50.0 (29.2)
AST (U/L)	47.9(31.6)	44.2(23.0)	53.8(18.2)	38.0 (20.7)	35.1 (17.7)
HDL-C (mg/dL)	44.8(8.7)	58.4(6.0)	41.5(6.3)	45.2 (13.4)	43.8 (12.5)
LDL-C (mg/dL)	116.0(25.4)	127.5(24.6)	122.61(25.1)	116.9 (30.0)	111.3 (30.4)
TG (mg/dL)	156.8(54.0)	180.4(74.3)	228.6(126.5)	161.1 (75.2)	178.5 (82.4)

除非特别说明，数据为平均数（标准差）或人数（%）

4 mg ASC41 QD demonstrated a statistically significant CFB of -32.6% in ALT (p=0.0051) and -24.2% in AST (p=0.041) vs placebo at week 12. In contrast, resmetrirom and VK-2809 did not show a statistically significant difference in ALT and AST vs placebo at week 12.[1,2] These data notably differentiate ASC41 from other THRβ agonists.

Safety data is presented in Table 3.

- AEs were similar among the cohorts receiving ASC41 tablet treatment versus the placebo.
- Levels of thyroid axis hormones, including TSH, FT3 and FT4 were relatively unchanged from baseline among the cohorts receiving ASC41 tablet treatment versus the placebo.
- Changes in vital signs and ECG were similar among patients receiving ASC41 tablet treatment versus placebo.

Conclusions

Significant reductions in Liver fat, ALT, AST and lipids as well as excellent safety and tolerability profile at week 12 warrant further clinical studies for ASC41 tablet.

Table 2. Changes from baseline (CFB) in LFC, liver enzymes and lipids biomarkers at week 12.

参数	安慰剂 (n = 14)	ASC41 片	
		2 毫克, 每日一次 (n = 13)	4 毫克, 每日一次 (n = 15)
肝脏脂肪含量较基线的相对变化平均值	-13.1%	-55.0% (p = 0.0001)	-68.2% (p < 0.0001)
肝脏脂肪含量降低≥30%的患者比例	21.4%	92.3% (p = 0.0002)	93.3% (p < 0.0001)
肝脏脂肪含量降低≥50%的患者比例	21.4%	46.2% (p = 0.24)	86.7% (p = 0.0004)
绝对肝脏脂肪含量≤5%的患者比例	0.0%	30.8% (p = 0.16)	66.7% (p = 0.0017)
ALT较基线相对变化平均值	5.2%	-8.5% (p = 0.61)	-32.6% (p = 0.0051)
ALT 降低> 17 U/L的患者比例	21.4%	30.8% (p = 0.68)	73.3% (p = 0.0052)
AST较基线相对变化平均值	17.3%	-3.6% (p = 0.67)	-24.2% (p = 0.041)
LDL-C较基线相对变化平均值	4.3%	-19.4% (p = 0.0002)	-23.4% (p < 0.0001)
TC较基线相对变化平均值	3.4%	-16.8% (p < 0.0001)	-20.0% (p < 0.0001)
TG较基线相对变化平均值	3.9%	-30.6% (p = 0.0001)	-42.6% (p < 0.0001)

Table 3. Safety data

事件, 数量(%)	安慰剂 (n = 14)	ASC41 片剂	
		2 毫克, 每日一次 (n = 13)	4 毫克, 每日一次 (n = 15)
治疗期出现的不良事件	13(92.9%)	13(100%)	15(100%)
药物相关TEAE	6(42.9%)	7(53.9%)	7(46.7%)
1级	6(42.9%)	7(53.9%)	7(46.7%)
药物相关的GI不良事件	2(14.3%)	3(23.1%)	1(6.7%)
恶心	0(0.0%)	0(0.0%)	0(0.0%)
呕吐	0(0.0%)	0(0.0%)	0(0.0%)
腹泻	1(7.1%)	3(23.1%)	1(6.7%)
腹胀	1(7.1%)	0(0.0%)	0(0.0%)
腹痛（上腹部）	0(0.0%)	0(0.0%)	0(0.0%)
便秘	0(0.0%)	0(0.0%)	0(0.0%)
消化不良	0(0.0%)	0(0.0%)	0(0.0%)
频繁排便	0(0.0%)	0(0.0%)	0(0.0%)

Authors' affiliation:
1. Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine; 2.The Affiliated Hospital of Hangzhou Normal University; 3.Affiliated Zhejiang Hospital, Zhejiang University School Medicine; 4. The First Affiliated Hospital of Wenzhou Medical University; 5. Nanfang Hospital, Southern Medical University; 6. Beijing Ditan Hospital Capital Medical University; 7. Sir Run Run Shaw Hospital, Zhejiang University; 8. Liaocheng People's Hospital; 9. Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; 10. Ruijin Hospital, Shanghai Jiaotong University School of Medicine; 11. Shanghai University of Traditional Chinese Medicine Shuguang Hospital; 12. Suzhou No.5 People's Hospital; 13. The Affiliated Hospital of Xuzhou Medical University; 14. Qingyuan People's Hospital; 15. Beijing Youan Hospital, Capital Medical University; 16. Xiangya Hospital, Central South University; 17. The First People's Hospital of Foshan; 18. The Third Affiliated Hospital,Sun Yat-Sen University; 19. Ningbo No.2 Hospital; 20. Zhongshan Hospital, Fudan University; 21. Peking University Shenzhen Hospital; 22. Beijing Friendship Hospital, Capital Medical University; 23. West China Hospital Of Sichuan University; 24. The Second Xiangya Hospital of Central South University; 25. The Second Affiliated Hospital of Guangzhou University Of Chinese Medicine; 26. The Second Affiliated Hospital, School of Medicine, Zhejiang University; 27. The First Affiliated Hospital of Nanchang University; 28. Shenzhen Third People's Hospital; 29. The First Hospital of Hebei Medical University; 30. The Second Hospital of Anhui Medical University; 31. Shijiazhuang Hospital of Traditional Chinese Medicine; 32. Guangzhou Eighth People's Hospital; 33. Taihe Hospital, Hubei University of Medicine; 34. Ningbo Medical Center Lihuili Hospital; 35. Meizhou People's Hospital; 36. Gannex Pharma Co., Ltd.

Abbreviation: ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL-C: low-density lipoprotein cholesterol; LFC: liver fat content; TC: total cholesterol; TG: triglyceride; AEs: adverse events; ECG: electrocardiogram; TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine.

Reference: [1]. Harrison, S. A., et al.[J] Lancet, (2019).DOI: 10.1016/s0140-6736(19)32517-6; [2]. Viking press release, May 2023