Significant Improvement of NAFLD Activity Scores and Liver Fibrosis by ASC42, a novel non-steroidal FXR agonist, in High Fat Diet Induced NASH mice

Xiaodong Li[1], Handan He[1], Eiketsu Sho[2], Jinhua Chen[1], Jinzi J.Wu[1]*.
1 Gannex Pharma Co., Ltd 2 Kci Biotech (Suzhou) Inc.

INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver condition evolving in a proportion of patients into nonalcoholic steatohepatitis (NASH), an aggressive form of NAFLD associated with increased cardiovascular mortality and significant risk of progressive liver disease, including fibrosis, cirrhosis and hepatocellular carcinoma. At present there is no approved medical therapy for NASH.
- Farnesoid X receptor (FXR) agonists have shown to benefit patients with non-alcoholic steatohepatitis.
- ASC42 is A novel non-steroidal, selective, potent FXR agonist and got fast track certification by U.S. FDA recently. ASC42's phase I clinical trial is currently being conducted in the United States.

AIM

- The objective of this study was to evaluate the therapeutic efficacy of ASC42 on high fat diet induced NASH model in male C57BL/6 mice with streptozotocin (STZ) and diethylnitrosamine (DEN) injection.

METHOD

- Mice injected with STZ and DEN were used to promote diabetes and liver fibrosis, respectively. Newborn mice received STZ injection on the 2nd day after birth. After a 2-week lactation, a DEN injection was given and followed by lactation for another 4 weeks.
- 10 newborn male mice receiving neither STZ nor DEN injection were defined as normal control animals. 50 male mice with STZ and DEN injection were randomly divided into 5 groups, the model+vehicle, comparator compound (OCA 30 mg/kg), ASC42 3 mg/kg, ASC42 10 mg/kg and ASC42 30 mg/kg.
- All rats were fed with HFD (60KCal% Fat + 1.25% Cholesterol + 0.5% cholate) by oral gavage for 8 weeks, and ASC42 and OCA were given 1 week after HFD feeding, once per day for 7 weeks.
- Livers were collected for pathological examination.

RESULT

- ASC42 demonstrated dose-dependently reductions in liver steatosis, inflammatory cell infiltration, ballooning change and total nonalcoholic fatty liver disease activity score (NAS). ASC42 at 30 mg/kg showed a significantly higher NAS reduction relative to OCA at 30 mg/kg ($P<0.001$) (Figure 1 and 2).
- ASC42 at 3 mg/kg showed a 46.2% reduction in NAS score and a 15.2% reduction in liver fibrosis, similar to OCA at 30 mg/kg (Figure 3 and 4).

CONCLUSIONS

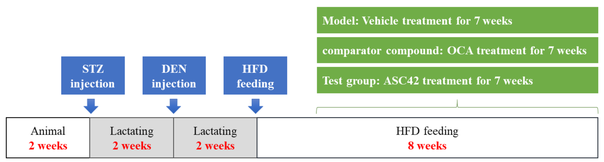
- ASC42 demonstrated NAS reductions and anti-fibrotic benefits in the STZ+DEN+HFD mouse NASH Model.
- These data supported the advancement of ASC42 into clinical trials in human.

CONTACT INFORMATION

- Gannex Pharma Co., Ltd.

Address: 3/F, 665 Zhangjiang Road, China (Shanghai) Pilot Free Trade Zone, Shanghai, China

Table 1, Experiment groups and dosing regimen



Group	Animal number	STZ-DEN-HFD	Dose	Treatment duration
Control	10	NO, vehicle	Vehicle	NA
Model	12	Yes	Vehicle	7 weeks
Positive (OCA)	12	Yes	30mg/kg	7 weeks
ASC42 (low dose)	12	Yes	3 mg/kg	7 weeks
ASC42 (medium dose)	12	Yes	10 mg/kg	7 weeks
ASC42 (high dose)	12	Yes	30 mg/kg	7 weeks

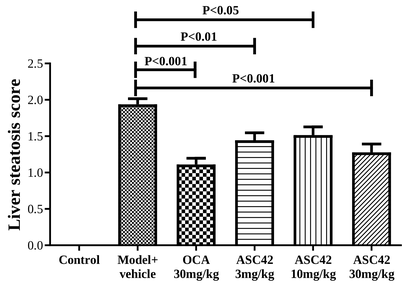


Figure 1 Improvement of Steatosis score after 7-week treatment

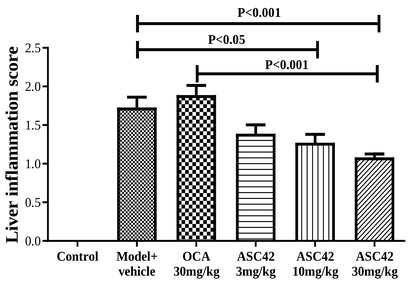


Figure 2 Improvement of Inflammatory cells infiltration score after 7-week treatment

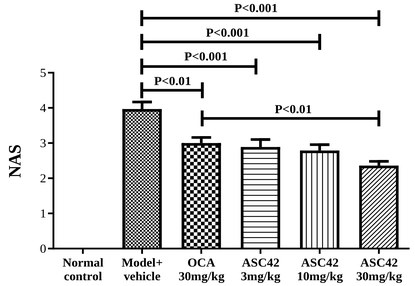


Figure 3 Improvement in NAS after 7-week treatment

NAS, nonalcoholic fatty liver disease activity score, was defined as the sum of steatosis, ballooning and inflammation score.

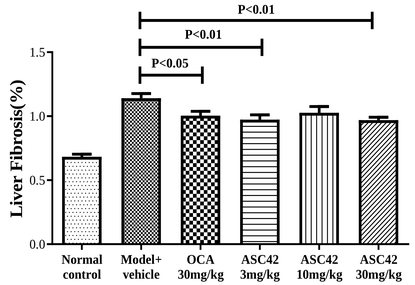


Figure 4 Improvement in fibrosis after 7-week treatment