Significant Improvement of NAFLD Activity Scores and Liver Fibrosis by ASC41, a Selective THR-β Agonist, in High Fat Diet Induced NASH SD Rats

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INTRODUCTION

- Thyroid hormone receptor β (THR-β) agonism has been reported to be an effective strategy to reduce low-density lipoprotein-cholesterol (LDL-C) and triglycerides for nonalcoholic steato hepatitis (NASH) treatment.
- ASC41, a small molecule prodrug, is selectively cleaved in liver by cytochrome P450 isozyme 3A4, to form a pharmacologically active metabolite ASC41-A, a potent THR-β agonist.
- A phase I clinical trial of ASC41 tablets conducted in China demonstrated significant reductions in LDL-C and triglycerides compared to placebo.

AIM

The objective of this study was to evaluate efficacy of ASC41 on high fat diet (HFD) induced NASH male SD rats with streptozotocin (STZ) and diethylnitrosamine (DEN) injection.

METHOD

- Rats injected with STZ and DEN were used to promote diabetes and liver fibrosis, respectively. Newborn rats received two STZ injections on the 2nd day and 7th day after birth, respectively. After a 2-week lactation, a DEN injection was given and followed by lactation for another 4 weeks.

METHOD

- 10 newborn male rats receiving neither STZ nor DEN injection were defined as normal control animals.
- 50 male rats with STZ and DEN injections were randomly divided into 5 groups as model + vehicle group, comparator group (MGL3196 5 mg/kg) , ACS41 0.5mg/kg, ACS41 1.5mg/kg, ACS41 4.5mg/k.
- All rats were fed with HFD (60KCal% Fat + 1.25% Cholesterol + 0.5% cholate) by oral gavage for 8 weeks, and ASC41 and MGL3196 were given 1 week after HFD feeding, once per day for 7 weeks. LDL-c were measured. Livers were collected for pathological examination.

REASULT

- Compared to the model group, ASC41 treatment groups at 1.5 and 4.5 mg/kg significantly reduced TC and LDL-c levels (Figure 1 and Figure 2).
- ASC41 demonstrated dose-dependently reductions in liver steatosis, inflammatory cell infiltration, ballooning change and total nonalcoholic fatty liver disease activity score (NAS). ASC41 at 1.5 mg/kg and 4.5 mg/kg showed higher NAS reductions relative to MGL3196 at 5 mg/kg (P=0.01 and P<0.001) (Figure 3).
- ASC41 at 0.5 mg/kg showed a 23.9% reduction in NAS score and a 14.4% reduction in liver fibrosis, similar to MGL3196 at 5 mg/kg (Figure 3 and Figure 4).

CONCLUSIONS

- ASC41 demonstrated NAS reductions and anti-fibrotic benefits in the HFD+DEN+STZ rat NASH Model. The current efficacy data supported the advancement of ASC41 into clinical trials in human.

CONTACT INFORMATION

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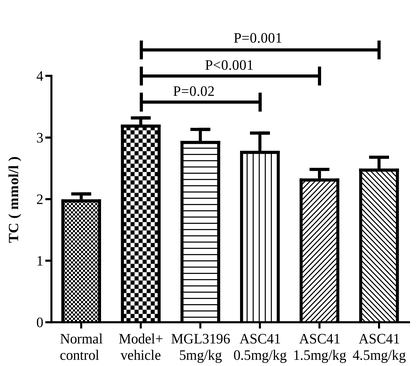

Figure 1 Clinical serum biochemical determination (TC)

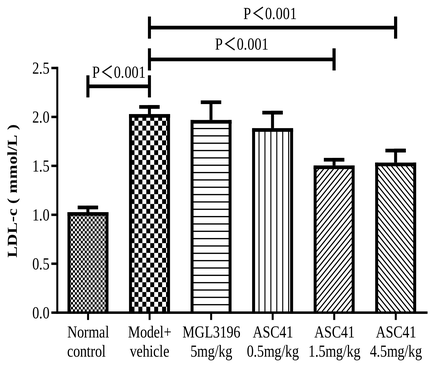

Figure 2 Clinical serum biochemical determination (LDL-c)

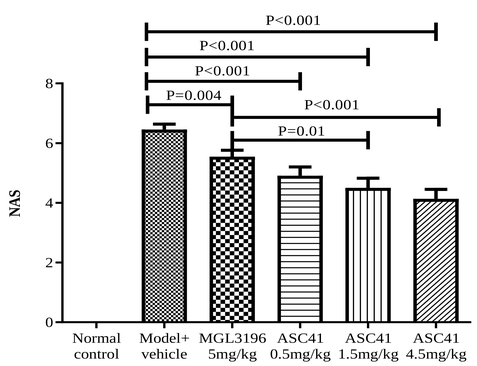

Figure 3 Improvement in NAS after 7-week treatment

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

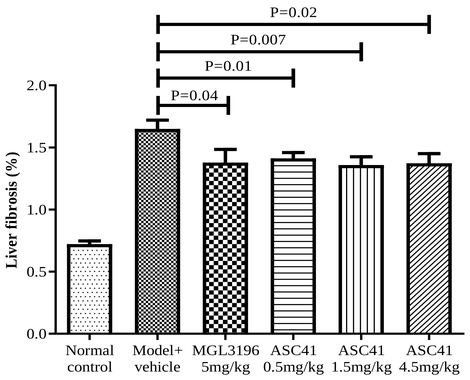

Figure 4 Improvement in fibrosis after 7-week treatment