Synergistic Effects of ECC4703, a Liver-targeting THRβ Full Agonist, in Combination with ECC0509, a Selective SSAO Inhibitor, or Semaglutide in a MASH Animal Model

Jianfeng Xu[1], Xuefeng Sun[1], Jingye Zhou[1,2]

Author affiliate: 1. Eccogene (Shanghai) Co., Ltd. 2. Eccogene Inc.

ECCOGENE

Poster ID 1064

AASLD The Liver Meeting®

Introduction and objectives

- Metabolic dysfunction-associated steatohepatitis (MASH, previously known as nonalcoholic steatohepatitis [NASH]) is a chronic, serious, life-threatening, inflammatory liver disease characterized by increased liver fat content, hepatocellular injury, inflammation, and progressive fibrosis. In view of the complexity of manifestation and serious nature of the disease, employing a combination of orthogonal mechanisms may be necessary to achieve optimal efficacy for the treatment of MASH.
- Eccogene is developing ECC4703, a selective THRβ full agonist, and ECC0509, a mechanism-based inhibitor of semicarbazide sensitive amine oxidase (SSAO). Both molecules have demonstrated favorable safety and tolerability profiles, PK and PD profiles supporting once daily dose, and clear target engagement in phase I clinical trials[1,2]. Additionally, Semaglutide has been approved to treat MASH in adults with moderate-to-advanced fibrosis recently[3].
- Here we evaluated the therapeutic potentials of ECC4703, ECC0509 and Semaglutide as mono-therapies or in combination of each other in a preclinical MASH model.

Methods

- The mouse MASH model was established by high-fat diet feeding and CCl4 induction, followed by 28-days treatment of Vehicle (G1), Semaglutide 10 nmol/kg (G2), ECC4703 3 mg/kg (G3), ECC0509 20 mg/kg (G4), ECC4703 3 mg/kg and Semaglutide 10 nmol/kg (G5) and ECC4703 3 mg/kg and ECC0509 20 mg/kg (G6), respectively. At the end of the study, the liver tissue was dissected for histology evaluation of NAFLD Activity Score (NAS) and fibrosis. Liver enzymes, liver cholesterol, triglyceride (TG), plasma cholesterol and LDL-C were also measured.

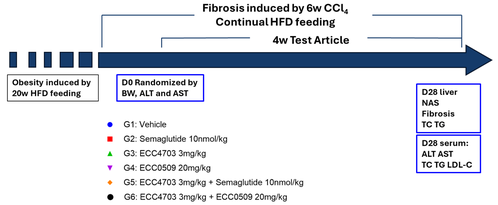
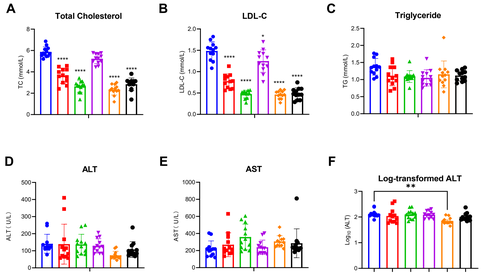


Figure 1. Study design scheme

Results

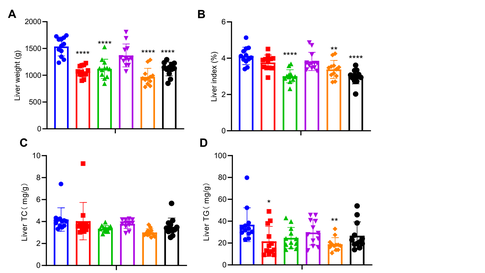
Serum biochemistry profile after treatment



N=10, Data presented as mean+/-SEM. For ALT, logarithm transformation was applied to reduce SD between groups.
, ** indicate p<0.01 or p<0.0001 vs. G1 Vehicle using one-way ANOVA followed by Dunnett's test.

Figure 2. Total cholesterol (A), LDL-C (B), triglyceride (C), ALT (D), AST (E), logarithm-transformed ALT (F). TC and LDL-C were significantly decreased in G2, G3 , G5 and G6. For serum ALT, ECC4703+Semaglutide treatment showed a decreasing trend despite large variability of the data and inconsistent standard deviations (SD) across groups. When data were Log-transformed to reduce SD differences, ALT is significantly decreased by ECC4703+Semaglutide treatment. No significant changes were observed for TG and AST.

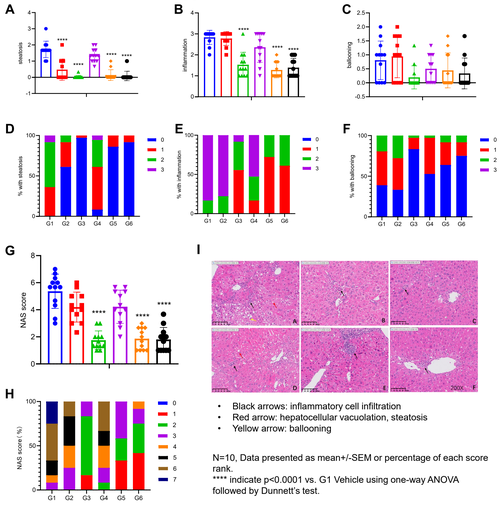
Liver weight and liver lipids



N=10, Data presented as mean+/-SEM.
*, **, **** indicate p<0.05, p<0.01 or p<0.0001 vs. G1 Vehicle using one-way ANOVA followed by Dunnett's test.

Figure 3. Liver weight (A), liver index (liver/body weight ratio, B), liver total cholesterol (C), liver triglyceride (D). Semaglutide, ECC4703, ECC4703+Semaglutide and ECC4703+ECC0509 resulted in significant reduction of liver weight compared to Vehicle. Liver TG was significantly reduced in Semaglutide alone or ECC4703+Semaglutide groups. When data were Log-transformed to reduce SD differences, liver TC was significantly decreased by ECC4703 alone or ECC4703+Semaglutide treatment, liver TG was significantly reduced by Semaglutide alone or ECC4703+Semaglutide treatment (figures not shown).

Liver histopathology and NAS scores

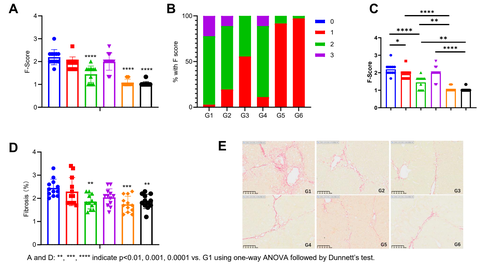


- Black arrows: inflammatory cell infiltration
- Red arrow: hepatocellular vacuolation, steatosis
- Yellow arrow: ballooning

N=10, Data presented as mean+/-SEM or percentage of each score rank.
**** indicate p<0.0001 vs. G1 Vehicle using one-way ANOVA followed by Dunnett's test.

Figure 4. Steatosis, inflammation, ballooning and NAS score in bar graphs (A, B, C, G) and stacked bar graphs (D, E, F, H), representative liver H/E staining (I).

Liver fibrosis



A and D: **, ***, **** indicate p<0.01, 0.001, 0.0001 vs. G1 using one-way ANOVA followed by Dunnett's test.

Figure 5. Liver fibrosis score in bar graph (A), stacked bar graph (B), statistical analyses by Mann-Whitney test (C), fibrosis area % (D) and representative Sirius Red staining (E). The fibrosis score of the combo therapy (G5 or G6) is significantly lower than related mono-therapies (G2 and G3, G3 and G4) by Mann-Whitney test, respectively.

Synergistic effects of combo-treatment

Parameters/Statistical method	G5 vs. G2	G5 vs. G3	G6 vs. G3	G6 vs G4
Fasting blood glucose	n.s.	p<0.01	n.s.	n.s.
Fasting insulin	n.s.	n.s.	n.s.	n.s.
Liver weight	p<0.0001	n.s.	n.s.	n.s.
Serum TC	p<0.0001	n.s.	n.s.	p<0.0001
Serum LDL-C	p<0.001	n.s.	n.s.	p<0.0001
ALT	n.s.	n.s.	n.s.	n.s.
ALT Log-transformed	n.s.	p<0.05	n.s.	n.s.
AST	n.s.	n.s.	n.s.	n.s.
Liver TC	n.s.	n.s.	n.s.	n.s.
Liver TC Log-transformed	p<0.05	n.s.	n.s.	n.s.
Liver TG	n.s.	n.s.	n.s.	n.s.
Liver TG Log-transformed	n.s.	n.s.	n.s.	n.s.
NAS-steatosis/ANOVA	n.s.	n.s.	n.s.	p<0.0001
NAS-steatosis/MW	n.s.	n.s.	n.s.	p<0.0001
NAS-inflammation/ANOVA	p<0.0001	n.s.	n.s.	p<0.0001
NAS-inflammation/MW	p<0.0001	n.s.	n.s.	p<0.01
NAS-ballooning/ANOVA	n.s.	n.s.	n.s.	n.s.
NAS-ballooning/MW	n.s.	n.s.	n.s.	n.s.
NAS-total/ANOVA	p<0.0001	n.s.	n.s.	p<0.0001
NAS-total/MW	p<0.0001	n.s.	n.s.	p<0.0001
Fibrosis-%fibrosis area	p<0.05	n.s.	n.s.	n.s.
Fibrosis-F-score/ANOVA	p<0.05	n.s.	n.s.	n.s.
Fibrosis-F-score/MW	p<0.0001	p<0.01	p<0.01	p<0.0001

Table 1. statistical analyses between combo vs mono-therapies. One-way ANOVA followed by Tukey's test was used from most comparison. Logarithm-transformation was applied when uneven SD between groups exists. For categorical variables, non-parametric Mann Whitney tests were applied as well.

ANOVA: one-way ANOVA, MW: non-parametric Mann Whitney test.

Conclusions

- THRβ agonist ECC4703 is effective to decrease liver NAS and fibrosis along with other metabolic benefits in this MASH model.
- The combination of ECC4703 with other mechanisms, i.e., Semaglutide or ECC0509, resulted in greater improvement compared to mono-agent treatment in fibrosis score and other metabolic and liver related endpoints, indicating the potential of ECC4703 as the corner stone for combination to treat MASH in humans.

Acknowledgement

We thank KCI Biotech for conducting the study and Eccogene team for constructive discussions.

Disclosure

All authors are employees and equity holders of Eccogene.

References: 1&2. Poster# 5019 & 5020, The Liver Meeting 2024, San Diego; 3. FDA website.