AASLD The Liver Meeting® Nov. 15-19, 2024

Poster No. 5019

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ECC4703, a Highly Selective Liver Targeting Thyroid Hormone Receptor-beta (THR-b) Full Agonist for MASH in a Phase 1 Trial

Samuel Pak[1], Laurie Butcher[2], Xuefeng Sun[3], Xiaoliang Pan[3], Bo Zhu[3], Haihui Liu[3], Wengang Chen[2], Jianfeng Xu[3], Jingye Zhou[2], Jianfeng Xu[2]

1 – PPD, United States. 2 – Eccogene Inc, United States. 3 – Eccogene (Shanghai) Co. Ltd,. China

ECCOGENE

INTRODUCTION

- Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic and life-threatening liver disease with increased fat content, hepatocellular injury, inflammation, and progressive fibrosis[1].
- Rezdiffra (MGL-3196), a THRβ agonist, is FDA-approved for treating MASH with moderate to advanced liver fibrosis[2]
- ECC4703, a novel small molecule, liver targeting full THRβ agonist, showed desired potency and selectivity as well as superior liver target engagement compared to MGL-3196. In MASH animal models, it improved liver NAS score, liver fibrosis and plasma lipids[3].

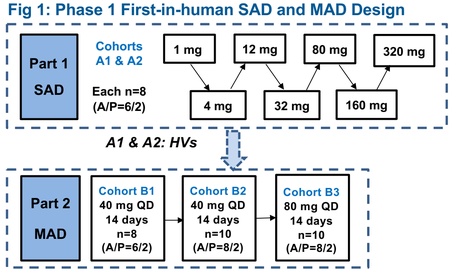
AIM

- To evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ECC4703 in a first-in-human study

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled, 2-part FIH phase I study investigated single and multiple ascending doses (SAD and MAD) of ECC4703 in healthy participants and those with mild LDL-C elevation (NCT05552274).

Fig 1: Phase 1 First-in-human SAD and MAD Design



- Part 1 SAD evaluated 7 ascending single doses of ECC4703 or placebo under fasted conditions in 2 cohorts, A1 (1 mg, 12 mg, 80 mg) & A2 (4 mg, 32 mg, 160 mg, 320 mg), each 8 participants (A/P=6/2).
- Part 2 MAD evaluated ECC4703 40 mg or 80 mg QD for 14 days under fasted conditions in 3 cohorts:
  - B1 at 40 mg in 8 healthy participants (A/P=6/2)
  - B2 at 40 mg and B3 at 80 mg each in 10 participants (A/P=8/2) with treatment-unnecessary LDL-C under 160 mg/dL
- Key Inclusion Criteria:
  - 18-65 years, body mass index (BMI) 18-32.0 kg/m^2
  - Part 2 B2 & B3: LDL-C ≥ 100 mg/dL and ≤ 159 mg/dL
- Key Exclusion Criteria:
  - Abnormal LFT
  - History of liver or thyroid diseases
- Primary Endpoints:
  - Safety and tolerability – adverse events (AEs), vital signs, physical exams, ECGs, clinical labs including thyroid hormones
- Secondary Endpoints:
  - PK parameters - AUC, C_{max}, T_{max}, $T_{1/2}$, Cl/F, V/F
  - PD - Sex Hormone Binding Globulin [SHBG] and lipid panel

RESULTS – SAD & MAD

DEMOGRAPHICS & BASELINES

- In SAD, 38 healthy participants including 6 replacements (3 due to TEAEs and 3 due to failure to meet continuation criteria) were randomized for 8 dosing periods. Of the 38 participants, 55.3% were male with mean (range) age of 41.7 (23-61) years and mean (SD) BMI of 26.0 kg/m^2 (3.1). Most participants were Non-Hispanic (81.6%).
- In MAD, 29 generally healthy participants including 1 replacement (due to TEAEs) were randomized in 3 cohorts. The baseline characteristics were generally similar across cohorts (Table 1).

Table 1: Part 2 MAD Demographics & Baseline Characteristics

MAD ECC4703	Pooled PBO	B1: 40 mg	B2: 40 mg	B3: 80 mg	Total
N	7	6	8	8	29
Age M (range)	43.9 (27-58)	39.7 (25-59)	52.3 (30-63)	38.0 (29-52)	43.7 (25-63)
Male, N (%)	4 (57.1%)	3 (50%)	5 (62.5%)	3 (37.5)	15 (51.7%)
Non-Hispanic, N (%)	4 (57.1%)	4 (66.7%)	6 (75.0%)	5 (62.5%)	19 (65.5%)
BMI (kg/m^2), M (SD)	26.1 (3.4)	27.6 (2.8)	26.9 (4.2)	24.8 (3.9)	26.3 (3.6)
LDL (mmol/L), M (SD)	3.154 (0.831)	2.952 (0.546)	3.044 (0.573)	3.329 (0.711)	3.161 (0.666)
TG (mmol/L), M (SD)	1.387 (1.131)	1.075 (0.503)	1.244 (0.291)	1.044 (0.330)	1.187 (0.622)
ApoB (mg/dL), M (SD)	97.4 (17.93)	94.5 (18.25)	92.9 (16.44)	93.1 (19.04)	93.4 (17.03)
HDL (mmol/L), M (SD)	1.601 (0.504)	1.320 (0.307)	1.258 (0.272)	1.375 (0.445)	1.384 (0.395)
HSBG (nmol/L), M (SD)	37.25 (14.031)	37.25 (14.031)	42.98 (24.274)	53.64 (24.826)	46.36 (21.15)

PBO = Placebo; M = mean; SD = Standard Deviation

SAFETY AND TOLERABILITY

- Overall, single and multiple doses of ECC4703 were well tolerated.
- No serious adverse events (SAEs) or deaths were reported.
- No clinically concerning ECG or lab findings were observed.
- No thyroid-related adverse events or significant changes in TSH and T3 were noted, with most thyroid hormone parameters remaining within normal range, despite a 20-30% reduction in TT4 and FT4 on Day 15 in MAD.

Table 2: Adverse Events in Part 2 MAD

MAD TEAEs n (%)	PBO n = 7	ECC4703 B1: 40 mg n = 6	ECC4703 B2: 40 mg n = 8	ECC4703 B3: 80 mg n = 8	Total n = 29
TEAEs	2 (28.6)	1 (16.7)	3 (37.5)	4 (50.0)	10 (34.5)
Leading to study drug discontinuation	1 (14.3)	0	0	0	1 (3.4)
Leading to death	0	0	0	0	0
SAEs	0	0	0	0	0
Study drug related	0	0	1 (12.5)	3 (37.5)	4 (13.8)
Transaminases increased	0	0	1 (12.5)	1 (12.5)	2 (6.9)
Pain in extremity	0	0	0	2 (25.0)	2 (6.9)

- TEAEs in MAD (Table 2):
  - 10 (34.5%) of 29 participants experienced 18 TEAEs, all mild
  - 1 placebo recipient discontinued due to as drug-unrelated TEAEs (chest pain and elevated BP)
  - No reports of diarrhea or pruritus
  - Common TEAEs (≥2 subjects): ALT increase (N=2; N=1 at 40 mg in B2, N=1 at 80 mg, drug-related), pain in extremity (N=2; N=2 at 80 mg, drug-related), headache (N=2; N=1 PBO, N=1 at 40 mg in B1, drug-unrelated)

PHARMACOKINETICS

- ECC4703 PK data demonstrated C_{max} and AUC increased with dose escalation in a lower than dose-proportional manner in SAD and in MAD (Fig 2, Table 3).
- PK parameters were similar in SAD and MAD: T_{max} of 3~4 hours post-dose and $t_{1/2}$ of 1.9~11.1 h (SAD) and 10.7~15.8 h (MAD).
- Steady state concentrations were achieved by Day 4 with an accumulation ratio of 1.008~1.24-fold between Day 1 and Day 14.

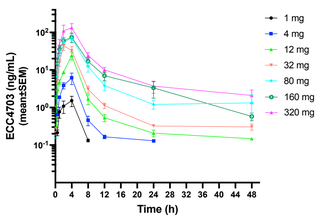


Fig 2: ECC4703 plasma exposure in SAD

Table 3: ECC4703 PK Parameters in SAD and MAD (Day 14)

PK Parameters	SAD (1 to 320 mg)	MAD (40 to 80 mg)
AUC(0-last) (ng*hr/mL)	5.4 to 873	157 to 322
C_{max} (ng/mL)	1.6 to 139	28.3 to 46.6
T_{max} (h)	3.0~4.0	4.0
$T_{1/2}$ (h)	1.9~11.1	10.7~15.8
CL/F (L/h)	126~429	176~277

AUC, C_{max}, $T_{1/2}$, CL/F: geometric mean, T_{max}: median (min, max)

PHARMACODYNAMICS: SHBG AND Lipids

- In MAD, following 14-day repeat doses of ECC4703, an up to 195.7% PBO-corrected increase in SHBG at the 40 mg dose were observed (Fig 3).
- 30 to 45% PBO-corrected reduction in LDL-C across 40 mg and 80 mg
- Other lipid replated biomarkers, including total cholesterol (12-24%), triglycerides (14-21%) & Apo-Lipoprotein B (23-28%) were found reduced by ECC4703 treatment on Day 15 (Table 4).

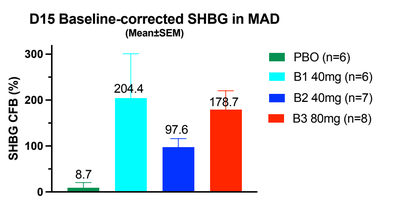


Fig 3: SHBG Increase and LDL-C Reduction on Day 15 in MAD

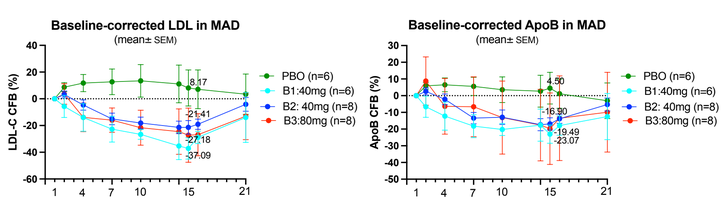


Fig 4: LDL-C and Apo-B time course on Day 15 in MAD

Table 4: ECC4703 PD Parameters in SAD and Steady State in MAD (Day 15)

Day 15 PCFB (%) mean (SD)	PBO n = 6	ECC4703 B1: 40 mg n = 6	ECC4703 B2: 40 mg n = 8	ECC4703 B1+2: 40 mg n = 14	ECC4703 B3: 80 mg n = 8
LDL (mmol/L)	8.175 (33.1146)	-37.094 (8.0309)	-21.414 (14.5192)	-28.134 (14.2535)	-27.180 (20.3661)
TG (mmol/L)	-14.735 (50.1105)	-28.924 (14.4519)	-35.721 (11.4248)	-32.808 (12.7593)	-31.429 (12.5990)
TC (mmol/L)	-4.978 (21.7656)	-29.247 (6.5472)	-16.965 (11.6059)	-22.229 (11.3488)	-21.627 (12.0481)
ApoB (mg/dL)	4.50 (23.14)	-23.07 (5.52)	-16.90 (10.42)	-19.54 (8.96)	-19.49 (19.88)
HDL (mmol/L)	-13.371 (14.9668)	-20.426 (12.3708)	-6.941 (16.3778)	-12.720 (15.8509)	-13.532 (8.9763)
SHBG (nmol/L)	8.70 (28.578)	204.43 (236.274)	97.56 (49.212)	146.89 (165.972)	178.72 (117.897)

PCFB: percentage change from baseline; SD: standard deviation; PBO: placebo

CONCLUSIONS

- The Phase 1 SAD and MAD study of ECC4703 in healthy participants and participants with treatment-unnecessary LDL-C under 160 mg/dL demonstrated a desirable safety and tolerability profile.
- ECC4703 PK profile supports once daily dosing strategy.
- ECC4703 effectively lowered a panel of atherogenic lipids, with significant LDL reduction observed over 14 days of treatment.
- The observed pharmacodynamic biomarker changes indicate clear target engagement.
- Overall, these data support the continued development of ECC4703 as a potential oral treatment for patients with MASH and dyslipidemia.

ACKNOWLEDGEMENTS

The authors and sponsor wish to thank the study participants for participating in this clinical study.

The Sponsor is grateful to the staff at PPD and PPD Early Phase Clinical Unit for their contribution to the study.

ThermoFisher SCIENTIFIC

REFERENCES

1. Saponaro, F. et al. Front Med (Lausanne) 2020; 7, 331.
2. Harrison SA. et al. NEJM. 2024; 390(6):497-509.
3. Hepatology 76: S638, October 2022
4. Charfi H. et al. Hepatology 78(S1): S1206, October 2023

DISCLOSURES

Pak, S.: none. Xu J., Sun X., Butcher L., Pan X., Liu H., Chen W., Zhou J., Xu J.: Eccogene employees and equity holders

CONTACT INFORMATION

Jianfeng Xu
(jianfeng.xu@eccogene.com)