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

Poster No. 5020

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ECC0509, an SSAO Inhibitor for MASH, in a Phase 1 trial

Angela Rowland[1], Jianfeng Xu[2], Xuefeng Sun[3], Laurie Butcher[2], Xiaoliang Pan[3], Haihui Liu[3], Wengang Chen[2], Jingye Zhou[2], Jianfeng Xu[3]

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

ECCOGENE

INTRODUCTION

- Semicarbazide-sensitive amine oxidase (SSAO) (or VAP-1, AOC3) catalyzes oxidative deamination of primary amines and mediates leukocyte adhesion and migration from blood to tissue.
- SSAO protein expression is upregulated in MASH patients and correlates with fibrosis stage and disease progression[1].
- SSAO inhibitors are demonstrated to be effective in reducing SSAO activity and improving liver injury biomarkers, ALT and caspase-cleaved CK-18, in patients with MASH[2].
- ECC0509 is an orally administered small molecule SSAO inhibitor with DDI concerns discharged and is in development for MASH.
- In non-clinical studies, ECC0509 was shown as a potent, highly selective and peripherally distributed SSAO inhibitor with minimal inhibition of brain AO[3].
- In a preclinical MASH model, 4-week administration of ECC0509 improved NAS score with reduced hepatocyte degeneration[3].

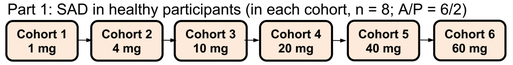
AIM

- To evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ECC0509 in a first-in-human study

MATERIALS AND METHODS

It was a randomized, double-blind, placebo-controlled, 2-part FIH phase I study to investigate single and multiple ascending doses (SAD and MAD) of ECC0509 in healthy participants (NCT05012423).

Part 1: SAD in healthy participants (in each cohort, n = 8; A/P = 6/2)



Part 2: MAD in healthy participants (in each cohort, n = 12; A/P = 8/2)

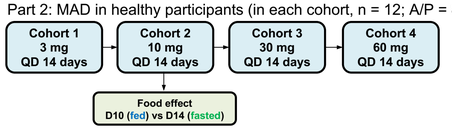


Fig 1: Phase 1 First-in-human SAD and MAD Design

- Key Inclusion Criteria:
  - healthy males or non-childbearing potential females
  - 18-65 years, body mass index (BMI) 18-32.0 kg/m^2
- Key Exclusion Criteria:
  - Current, or history of, major medical conditions
- Primary Endpoints:
  - Safety and tolerability – AEs, vital signs, physical exams, ECGs, Labs
- Secondary Endpoints:
  - PK parameters
  - PD - plasma SSAO activity; plasma methylamine

RESULTS

DEMOGRAPHICS AND DISPOSITION

- In SAD, mean age was 36.0 years and mean BMI was 25.72 kg/m^2 with most participants white and non-Hispanic. All completed the study.
- In MAD, mean age was 34.2 years and mean BMI was 25.45 kg/m^2 with most participants were white and non-Hispanic. Two participants discontinued the study due to COVID infection (Cohort 2) and withdrawal of consent (Cohort 4), respectively.

SAFETY AND TOLERABILITY

- Single and multiple doses of ECC0509 were well tolerated.
- No discontinuations were due to study drug related adverse events (AEs).
- No clinically significant changes in ECGs or lab tests were observed.
- No drug-related SAEs were reported in SAD and MAD.
- **Treatment Emergent AEs (TEAEs) In SAD**
  - All the 24 TEAEs reported in 17 (35.4 %) of 48 participants were mild.
  - 8 TEAEs in 7 (14.6%) participants were possibly/probably drug-related.
  - The most common AEs were headache (n=3) and abdominal pain (n=2).

Table 1: Summary of TEAEs in Part 2 MAD

MAD TEAEs n (%)	PBO n = 8	ECC0509 3 mg n = 8	ECC0509 10 mg n = 8	ECC0509 30 mg n = 9	ECC0509 60 mg n = 8	Total n = 41
TEAEs	6 (75.0)	3 (37.5)	6 (75.0)	5 (55.6)	3 (37.5)	23 (56.1)
Deaths	0	0	0	0	0	0
SAEs	0	0	0	0	1 (12.5)	1 (2.4)
Drug-related TEAEs with n ≥ 2						
Headache			1 (12.5)		2 (25.0)	3 (7.3)
Fatigue	1 (12.5)				2 (25.0)	3 (7.3)

TEAEs in MAD

- 23 (56.1 %) of 41 participants reported 58 TEAEs;
- 54 (93.1%) of TEAEs were mild; there was only 1 (1.7%) moderate TEAE in a participant who received placebo in MAD
- 1 participant in Cohort 4 withdrew consent and later reported drug-unrelated SAEs.
- 2 participants in Cohorts 2 & 3 discontinued study due to mild drug-unrelated TEAEs;
- 17 TEAEs in 7 (17.1%) participants were deemed related study drug.
- The most common AEs were headache (n=3) and fatigue (n=3).

PHARMACOKINETICS

- ECC0509 demonstrated a linear and dose-dependent increase in C_{max} and AUC in SAD and in MAD (Fig 2).
- PK parameters were similar in SAD and MAD: T_{max} of 2~4 hours post-dose and $T_{1/2}$ of 3~4.5 hours.
- Steady state concentrations were achieved by Day 4 with an accumulation ratio of 1.7~2.8-fold between Day 1 and Day 14.
- Exploratory evaluation of food effect indicated minimum increase in $C_{max,ss}$ and $AUC_{0\text{-last}}$ (GMR of 1.288 and 1.473, respectively) post moderate fat meal vs fasted conditions, suggesting no significant food effect.

ECC0509 in SAD (mean±SEM) | ECC0509 in MAD (mean±SEM)

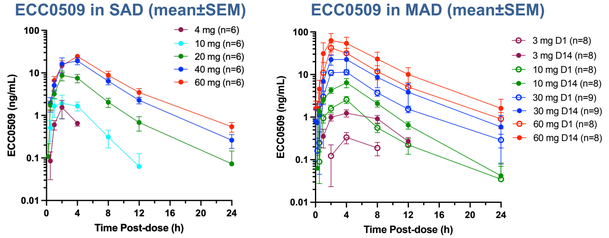


Fig 2: Plasma ECC0509 Concentrations in SAD and MAD

PHARMACODYNAMICS

SSAO in MAD (mean±SEM) | SSAO in MAD (mean±SEM)

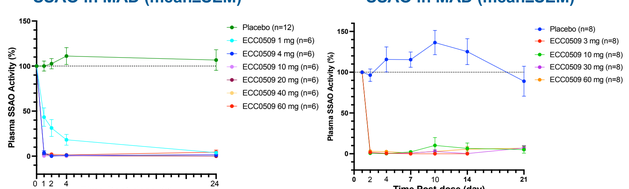


Fig 3: Plasma SSAO Activity in SAD and MAD

SSAO specific activities in plasma samples were determined in the presence of MAO and DAO inhibitors using benzylamine as substrate. Data were normalized to pre-treatment baseline

- In SAD, ECC0509 potently inhibited plasma SSAO activity starting from 1 h post-dose and reaching nearly complete inhibition by 24 h post-dose across all doses.
- In MAD, a nearly complete inhibition of SSAO activity occurred on Day 2 across all doses (3 mg to 60 mg), and remained through 14-day treatment and up to Day 21 follow-up visit.

Methylamine in SAD (mean±SEM) | Methylamine in MAD (mean±SEM)

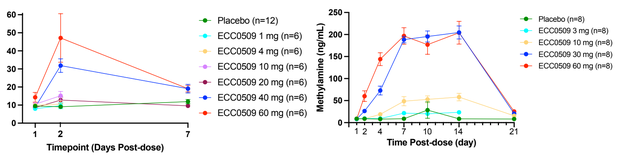


Fig 4: Plasma Methylamine in SAD & MAD

- Methylamine (MA) is the endogenous SSAO substrate and its accumulation in plasma generally reflects whole body SSAO inhibition
- In SAD and MAD, plasma MA increased dose dependently on Day 2 and nearly returned to baseline 6~7 days post last dose.
- In MAD, MA accumulated over treatment days and reached static state on Day 7.
- Maximal increase in MA was observed at once daily doses 30 mg and above in MAD, indicating inhibition of SSAO activities in most tissues at 30 mg and providing evidence for dose options in Ph2 studies.

CONCLUSIONS

- ECC0509 is a small molecule, oral, once-daily, selective and peripherally distributed SSAO inhibitor.
- The Phase 1 SAD and MAD study of ECC0509 in healthy participants demonstrated a desirable safety and tolerability profile.
- Plasma SSAO activity was nearly completely inhibited by low doses of ECC0509, whereas plasma methylamine increased dose-dependently and plateaued at 30 mg.
- Overall, these data support continued development of ECC0509 as a potential oral once-daily therapy for patients with MASH.

ACKNOWLEDGEMENTS

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

The Sponsor is grateful to the staff at Syneos Health and CMAX for their contribution to the study.

Disclosure

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

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Contact

Jianfeng Xu (jianfeng.xu@eccogene.com)