ECC0509，a novel peripherally distributed and selective semicarbazide-sensitive amino oxidase (SSAO) inhibitor for NASH treatment

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DIGITAL EXPERIENCE

Introduction

Non-alcoholic steatohepatitis (NASH) is metabolic-related liver disease featured with ectopic fat accumulation, hepatocellular damage, chronic inflammation, and progressive fibrosis. SSAO (VAP-1, AOC3) inhibitor is a potential therapy for NASH by suppression of inflammation and fibrosis progression. The clinical development of SSAO inhibitor BI 1467335 due to interf for NASH was discontinued erence with brain monoamine oxidase B (MAO-B) [1]. Therefore, a selective and peripherally distributed SSAO inhibitor is desired for testing this mechanism.

Aim

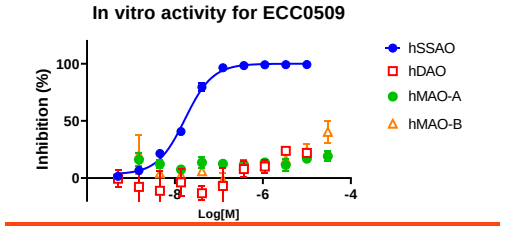
To evaluate ECC0509 as a novel SSAO inhibitor for NASH treatment

Materials and Methods

SSAO, MAO-A/B and diamine oxidase (DAO) activities were evaluated in enzymatic assays based on the oxidation of the luminogenic amine substrate in the MAO-Glo™ assay kit (Promega). Plasma/liver SSAO and brain total amine oxidase activities were evaluated in rats after oral administration of ECC0509. Plasma ALT, NALFD activity score (including steatosis, ballooning and inflammation) and %fibrosis area were evaluated in STAM NASH model following 4-week treatment of ECC0509. Liver tissue was collected for gene expression analysis.

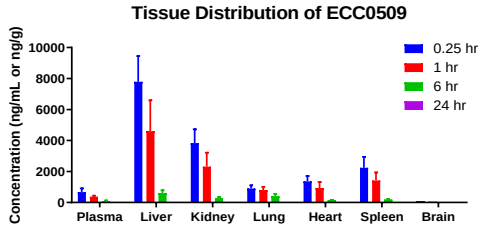
Results

Figure 1. ECC0509 is a potent and selective irreversible SSAO inhibitor.



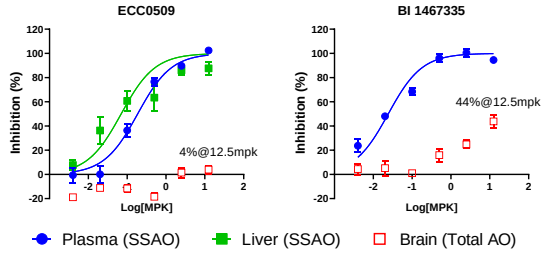
Enzyme IC50 (uM)	BI1467335	Tern-201[2]	ECC0509
hSSAO	0.022	0.011	0.020
hDAO	8.3	0.9	6.6
hMAO-A	>30	>50	>30
hMAO-B	3.0	>200	16.6

Figure 2. ECC0509 distributed in liver while has minimal brain exposure.



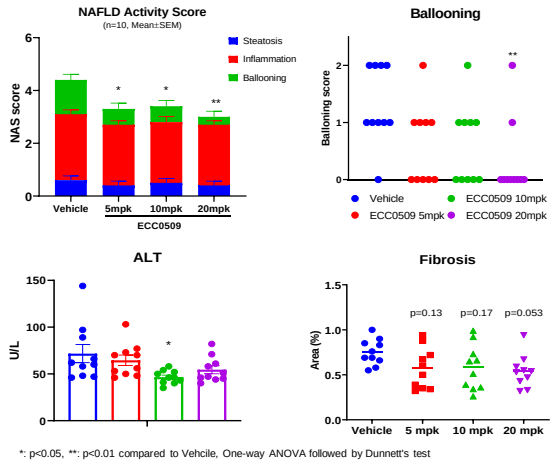
Tissue / plasma ratio						
Time post dosing (h)	Liver	Kidney	Lung	Heart	spleen	brain
0.25	12	5.7	1.3	2.0	3.3	0.029
1	12	6.3	2.2	2.5	3.8	0.053
6	6.4	2.5	2.9	1.1	1.7	0

Figure 3. ECC0509 has robust liver/plasma SSAO inhibition with no effects on amine oxidases in brain.



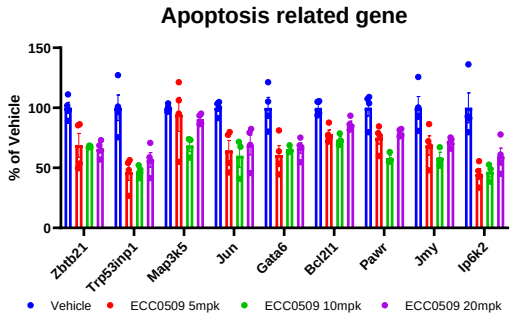
Plasma, liver and brain tissue were collected 24h post single dose of ECC0509 in SD rat. Plasma and liver SSAO activity were measured in the presence of MAO and DAO inhibitors. Brain amine oxidase activity was measure without MAO and DAO inhibitors

Figure 4. ECC0509 improved NAS score, plasma ALT and showed trend of reduced %fibrosis area.



*: p<0.05, **: p<0.01 compared to Vehcile, One-way ANOVA followed by Dunnett's test

Figure 5. ECC0509 significantly suppressed apoptosis related gene expression in liver tissue from STAM model.



Conclusions

- ECC0509 demonstrated optimal selectivity and tissue distribution, with complete inhibition of plasma and liver SSAO while no detectable inhibition on brain amine oxidase activity. ECC0509 also has minimal inhibition to DAO, a histamine metabolic enzyme.
- In a preclinical NASH model, 4-week administration of ECC0509 demonstrated improved NAS score with reduced degeneration and apoptosis biomarkers.
- ECC0509 is a potential best-in-class SSAO inhibitor and currently in phase I clinical trial.

References

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