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Poster-094

A Small Molecule Glucose Dependent Insulinotropic Peptide Receptor Antagonist for Treating Obesity

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Introduction and objectives

- GLP-1 receptor agonists (GLP-1RAs) are well validated mechanisms to treat type 2 diabetes (T2D), obesity and its related comorbidities.
- Tirzepatide, a dual GLP-1R and GIP receptor (GIPR) agonist, and Maridebart cafraglutide (as known as MariTide or AMG133), a GIPR antibody fused with peptide GLP-1RA, both demonstrated robust reduction of body weight in humans. These results support combination of a GIPR modulator with GLP-1RA to further enhance the therapeutic effects.
- Here we present the preclinical pharmacology and pharmacokinetics profile of a small molecule GIPR antagonist ECC-X for the treatment of obesity and related metabolic comorbidities.

Methods

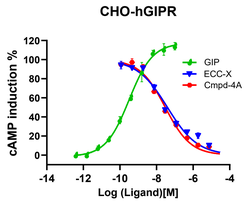
- We used CHO cells with overexpression of human, mouse and monkey GIPR, or human glucagon receptors to evaluate the cellular activities by cAMP accumulation.
- Mice with human-GIPR knocked-in were used to evaluate the effects on glucose excursion during intraperitoneal glucose tolerance test (ipGTT).
- Pharmacokinetics was profiled in rats after intravenous and oral administration.
- Mice with human-GIPR knocked-in were induced to achieved obese phenotype by 60% high-fat diet feeding. ECC-X was given once daily by oral gavage at 60 mg/kg, or 6 and 20 mg/kg in combination with semaglutide 10 nmol/kg for 28 days. Body weight and food intake were measured every day, body composition was measured at the baseline and after 28-day treatment.

References

1. Sattar N, et al., Diabetes Obes Metab. 2025 Oct;27(10):5386-5392.
2. Jastreboff AM, et al., N Engl J Med. 2025 Sep 4;393(9):843-857.

Results

ECC-X is a potent and selective antagonist for human, mouse and monkey GIP receptors



Compound No.	Cmpd-4A	ECC-X
Human GIPR (IC50, M)	4.92E-08	5.40E-08
Mouse GIPR (IC50, M)	6.77E-07	8.84E-07
Monkey GIPR (IC50, M)	2.7E-09	6.18E-09
hGCGR (IC50, M)	>5.0E-6	>5.0E-6
Selectivity over hGCGR	>100	>100

Figure 1. In vitro activities of ECC-X against human, mouse and monkey GIP receptors and human GCG (glucagon) receptors. Cmpd-4A is compound 4A from WO 2025/158275 A1. A typical result of cAMP accumulation in CHO-hGIPR cells is on the left, and summary of cellular activities is on the right.

ECC-X dose-dependently reversed GIP-induced suppression of glucose excursion in mice ipGTT

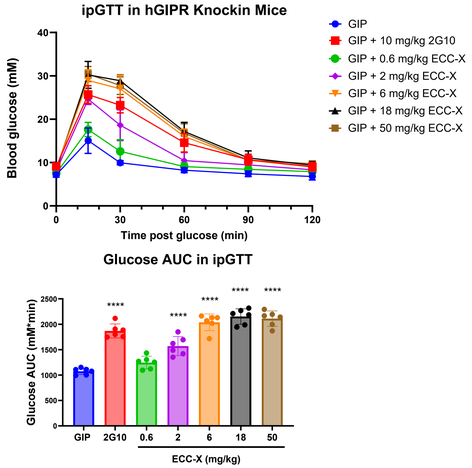
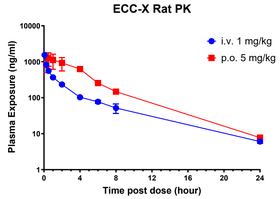


Figure 2. Glucose time course and AUC during ipGTT in human GIPR knockin mice. 2G10 is an antagonist antibody served as the positive control. Compound was dosed 2-hour (24-hour for 2G10) prior to GIP dosing, and intraperitoneal glucose challenge was given 2-hour later. Data presented as mean+/-SEM, n=5.

Pharmacokinetics of ECC-X in rats



PK pamameter	ECC-X
T1/2 (hr)	4.92
CL (mL/min/kg)	7.44
Vss (L/kg)	1.88
i.v. AUC0~t (1mpk, ng*hr/mL)	2210
p.o. AUC0~t (5mpk, ng*hr/mL)	6468
Bioavailability (%)	57.7

Figure 3. Pharmacokinetics profile of ECC-X in rats. Time course curves are presented on the left. PK parameters are listed on the right.

ECC-X in combination with semaglutide resulted in additional reduction of body weight and food intake in hGIPR knockin DIO mice

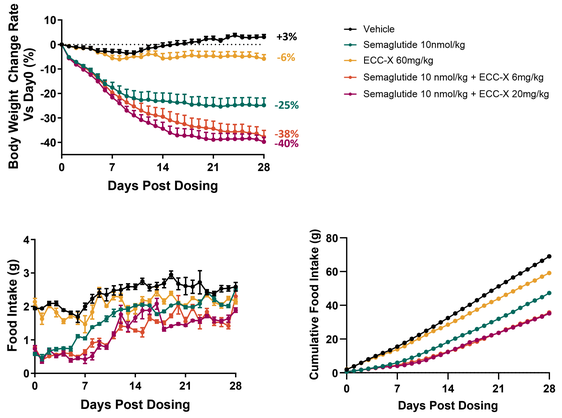


Figure 4. Percentage change from baseline of body weight on the top. Daily and cumulative food intake on the bottom. 60 mg/kg ECC-X was chosen to explore stand-alone efficacy. Two lower doses of ECC-X (6 and 20 mg/kg) were co-administered with 10 nmol/kg semaglutide to explore combinatory efficacy. Mild reduction of body weight and food intake was observed by ECC-X alone. The combination treatment resulted in greater weight loss and more sustained food intake reduction. Data presented as mean+/-SEM, n=10.

Body composition, liver and white adipose tissue weight indicated robust fat mass loss

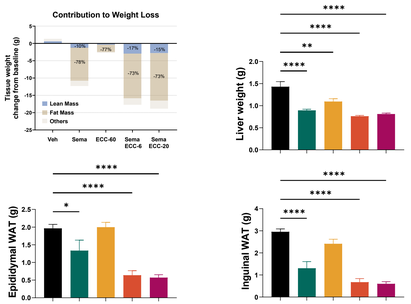


Figure 5. Body composition at Day28 and terminal tissue weight. Liver weight and white adipose tissue (WAT) were significantly reduced in semaglutide and the combination treatment groups. ECC-X alone mildly reduced liver weight. For tissue weight, data presented as mean+/-SEM, n=6.

Conclusions

- ECC-X is a potent antagonist for human, mouse and monkey GIP receptors, with good selectivity against human glucagon receptor.
- In human-GIPR KI mice, ECC-X dose-dependently reversed GIP-induced suppression of glucose excursion in ipGTT test.
- Pharmacokinetics profile of ECC-X is potential to achieve once daily dosing in humans.
- In diet-induced obese human-GIPR KI mice, ECC-X mildly reduced body weight and food intake by itself. When in combination with semaglutide, 6 and 20 mg/kg ECC-X treatment resulted in additional weight reduction along with more sustained appetite suppression.
- ECC-X demonstrated desired preclinical pharmacology and pharmacokinetics profiles, with therapeutic potential to treat obesity and related comorbidities.

Acknowledgement

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