A Unimolecular Incretin and Amylin Poly agonist for Treating Obesity

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Introduction and Objectives

- Obesity is now globally pandemic, leading to cardiometabolic comorbidities and socio-economic burden. GLP-1 based medical intervention is considered as one of the most effective ways to treat obesity[1] on top of life-style management.
- GLP-1 receptor agonists not only reduce hyperglycemia and body weight but also provide benefits in many obesity-related disorders, such as cardiovascular disease, chronic kidney diseases, obstructive sleep apnea, OA pain, et al.[2] Meanwhile, gastrointestinal adverse effects and weight rebound remain obstacles for long term treatment. Further improvement in weight management therapies would require either greater efficacy or address current therapies' limitations.
- Here we investigated a unimolecular peptide (**ECC10216**) with agonism over GLP-1, GIP, Amylin3 and Calcitonin receptors. The molecule bears favorable and balanced potency in cell-based assay. In lean rats, it demonstrates dose-dependent reductions in food intake and body weight, and appears more potent than Amycretin. In diet-induced obese (DIO) rats, it showed robust weight reduction superior to Amycretin and Semaglutide/ Cagrilintide combination. These results indicate the potential utility for anti-obesity treatment and long-term weight management.

Methods

- HEK293T cell lines with overexpression of human GLP-1, GIP, Amylin3 and Calcitonin receptors were used to evaluate the *in vitro* cellular activities.
- Lean Sprague Dawley (SD) rats (350-400g, n=5 per group) were treated single subcutaneous dose of Vehicle, Amycretin at 10 nmol/kg and ECC10216 at 1, 3 and 10 nmol/kg to investigate the effects on food intake reduction and body weight over 3-day period.
- DIO rats (~720g, n=8 per group) were subcutaneously administered with Vehicle, Amycretin at 10 nmol/kg daily, Semaglutide at 10 nmol/kg daily + Cagrilintide at 10 nmol/kg once every other day, or ECC10216 at 10 nmol/kg daily for 21 days. Body weight and food intake were measured daily, and body composition was measured by use of qNMR at baseline and day 21, the end of treatment. Visceral and subcutaneous adipose tissue were collected and weight at the end of the study.
- Statistical analyses were performed using one-way ANOVA followed by Dunnett's or Tukey's test if applicable in Prism.

Results

ECC10216 is a potent agonist against 4 receptors with balanced agonism

EC50 (pm)	hGLP1R	hGIPR	hAmy3R	hCTR
hGLP1 (n=4)	11.7	-	-	-
hGIP (n=4)	-	125.8	-	-
Tirzepatide (n=4)	49.4	439.0	-	-
Amycretin (n=4)	9.57	-	166.5	6.74
ECC10216 (n=4)	**18.3**	**25.4**	**16.9**	**9.24**
Cagrilintide (n=4)	-	-	15.3	17.7
Eloralintide (n=4)	-	-	34.1	24.3
Pramlintide (n=4)	-	-	4.09	35.3
hCalcitonin (n=4)	-	-	2842	3.55

Table 1. *In vitro* activities of **ECC10216** over human GLP-1 receptor, human GIP receptor, human Amy3 receptor and human calcitonin receptor. Related compounds are also included as references.

ECC10216 dose-dependently reduces body weight and food intake in lean rats

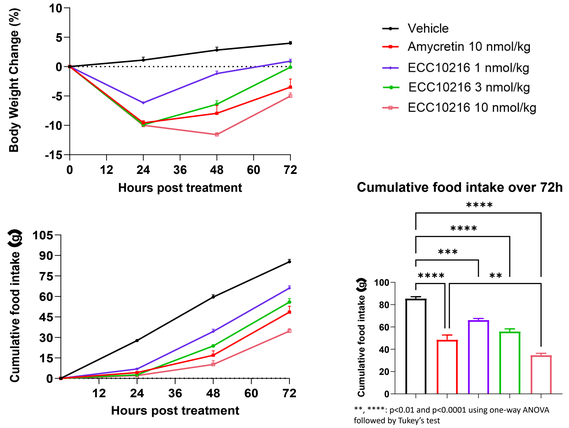


Figure 1. Body weight ad food intake in lean SD rats (n=5) after single subcutaneous administration. **ECC10216** dose-dependently reduced food intake and body weight and appeared more potent than Amycretin at the same dose. Data presented as mean ± standard error of the mean.

ECC10216 reduces body weight and food intake in DIO rats

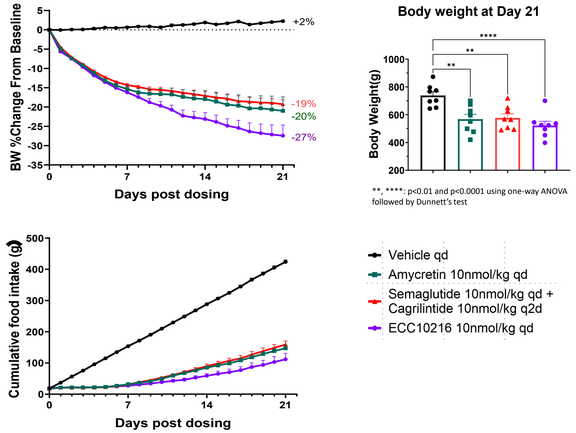
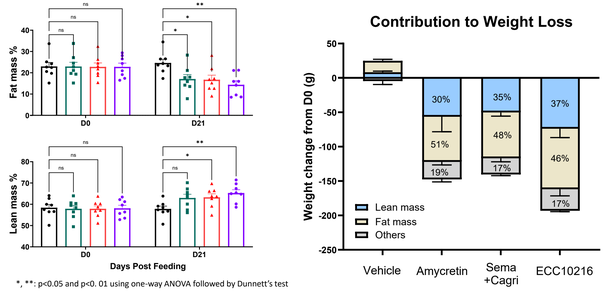


Figure 2. Body weight and food intake suppression in DIO rats (starting BW ~720g, n=8) after chronically subcutaneous dose at for 21 days. The efficacy of **ECC10216** appears greater than Amycretin and the combination of Semaglutide and Cagrilintide. Data presented as mean ± standard error of the mean.

ECC10216 preferentially reduces fat mass after chronic treatment



*, **: p<0.05 and p<0. 01 using one-way ANOVA followed by Dunnett's test

Figure 3. Body composition measured by qNMR before and after 21-day treatment. The percentage of fat mass was significantly decreased while the percentage of lean mass was significantly increased by **ECC10216.** Fat mass reduction accounted for ~50% weight loss by the treatment. Data presented as mean ± standard error of the mean.

ECC10216 treatment resulted in robust reduction of visceral and subcutaneous white adipose tissue

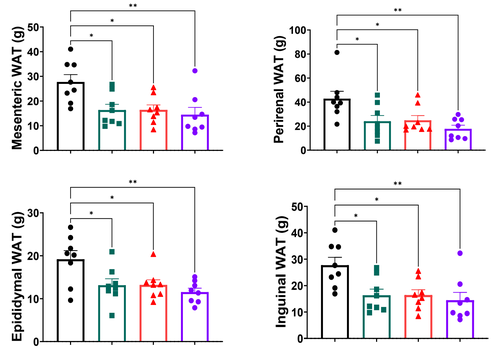


Figure 4. Adipose tissue weight after 21-day chronic treatment

Conclusions

- ECC10216 exhibits potent and balanced activities over 4 receptors.
- ECC10216 substantially reduced body weight and food intake in lean SD rat in a dose dependent manner.
- ECC10216 produced progressive BW reduction in DIO rat after 3-week chronic treatment with no sign of a plateau.
- ECC10216 showed preferential fat mass loss during weight loss in DIO rats.
- ECC10216, a unimolecular poly agonist combining GLP-1, GIP, Amylin and calcitonin receptor agonisms, demonstrated a proof-of-concept profile for weight management in preclinical models.

References

1. Lancet 2024, 404: 10456, 972-987;
2. N Engl J Med 2021, 384:11, 989-1002;

Acknowledgement

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