Amylin analog ZP8396 can be co-formulated with semaglutide to provide additive anti-obesity effect in the DIO rat model

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OBJECTIVES

- **To evaluate stability and aggregation of a coformulation of the long-acting amylin agonist ZP8396 and the GLP-1 agonist semaglutide (SEMA)**
- **To assess the effect of ZP8396 and SEMA alone and in combination on body weight and food intake in diet-induced obese (DIO) rats**

CONCLUSIONS

- **ZP8396 is equally stable alone and in co-formulation with SEMA at a physiologically relevant pH range**
- **Co-formulated ZP8396/SEMA shows comparable effect to the combination therapy and is superior to each monotherapy demonstrating significant weight loss**
- **ZP8396 is a potent long-acting amylin analogue currently being studied in Phase 1 clinical trials**

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INTRODUCTION

- Co-formulations of anti-obesity drugs hold great potential for weight management while maintaining a positive safety and tolerability profile.
- ZP8396 is a long-acting amylin analogue designed to improve solubility, minimize fibrillation and allow for co-formulation with other peptide anti-obesity drugs including GLP-1 agonists.
- Co-formulation is expected to provide added efficacy due to different mechanisms of action.
- ZP8396 induces significant weight loss in pre-clinical obesity models as monotherapy.
- SEMA is a once-weekly GLP-1 agonist approved for weight management for adults with obesity.

METHODS

- Accelerated stability for 1 mg/mL formulations of ZP8396 alone or in combination with 1 mg/mL SEMA was evaluated over 4 weeks storage at 40ºC in Type 1 glass vials. Chemical stability was evaluated by decrease in purity measured by RP-HPLC. Aggregation over time was evaluated by peptide particle size (Z-average) by Dynamic Light Scattering (DLS).
- DIO rats were treated from day 0 to day 13 with either vehicle or SEMA 8 nmol/kg by once daily (qd) sc injection. From day 14 to day 34 vehicle-treated rats continued either on vehicle or were switched to ZP8396 10 nmol/kg qod. From day 14 to day 34 SEMA-treated rats continued either on SEMA 8 nmol/kg qd or switched to the combination treatment of SEMA 8 nmol/kg qd plus ZP8396 10 nmol/kg qod or a co-formulation of ZP8396 5 nmol/kg/SEMA 8 nmol/kg qd or a co-formulation of ZP8396 10 nmol/kg/SEMA 16 nmol/kg qod.
- The anti-obesity effects were assessed by measurement of body weight and food intake.

RESULTS

ZP8396 is equally stable alone and in co-formulation with SEMA at a physiologically relevant pH range
Chemical stability is mainly impacted by pH and formulation composition, not the presence of SEMA.
No aggregation detected (4 weeks at 40ºC).

Peptide(s)	Formulation[1]	pH	Chemical degradation of ZP8396 (relative rate)	Aggregation (average peptide particle size)
ZP8396	TRIS buffer, sodium chloride **(#1)**	6.7	1.0	No aggregation[2]
ZP8396 + SEMA	TRIS buffer, sodium chloride	6.7	1.1	No aggregation[2]
ZP8396	Phosphate buffer, propylene glycol, phenol	7.4	1.8	No aggregation[2]
ZP8396 + SEMA	Phosphate buffer, propylene glycol, phenol	7.4	1.8	No aggregation[2]
ZP8396 + SEMA	Phosphate buffer, mannitol	7.1	1.4	No aggregation[2]

[1] Physiological compatible tonicity [2] No increase in average peptide particle size. All Z-averages ≤ 5 nm

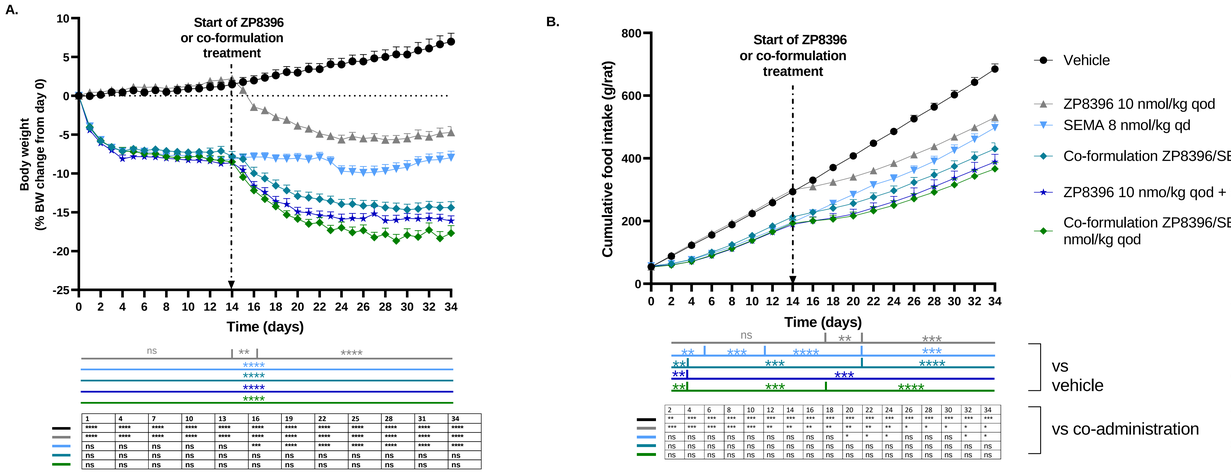
Table 1: Accelerated stability (4 weeks at 40ºC) for 1 mg/ml ZP8396 alone or co-formulation with 1 mg/mL SEMA. Relative rate of chemical degradation is calculated by: Relative rate = (Rate of purity decrease for Formulation X) / (Rate of purity decrease for Formulation #1). Aggregation evaluated by DLS.

Due to differences in the pharmacokinetics when dosed sc to rats of ZP8396 and SEMA different dosing regimens of either qd (SEMA) or qod (ZP8396) were required

	SC parameters	
	$T_{½}$, (h, Mean)	T_{max} (h, Median)
ZP8396	34	24
SEMA	10	4

Table 2: Pharmacokinetics of ZP8396 and SEMA in rats (n=3)

Combined treatment of ZP8396 and SEMA by co-administration or co-formulation demonstrated significant reduction of body weight and food intake in DIO rats compared to both vehicle- and each mono-treated group.



*Data are mean values with SEM (n= 10/group). Data were compared by 2-way ANOVA followed by Dunnett's multiple comparison test.
*The solid lines represent significant difference of co-formulation vs. vehicle group, **p<0.01, ***p<0.001, ****p<0.0001. The table graph represents significant difference of co-formulation vs. combination treatment with SEMA and ZP8396 group, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns=not significant*

Figure 1: Body weight change from day 0 (%) (A), cumulative food intake (B).

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