Anti-obesity Effects of GIP Analogue ZP6590 in Combination with Semaglutide in DIO Mice

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AIM

- **The aim of the study was to investigate the combined anti-obesity effects of the long-acting GIP analogue ZP6590 and semaglutide (SEMA) in diet-induced obese (DIO) mice**

CONCLUSIONS

- **The long-acting GIP analogue ZP6590 potentiated the benefits of SEMA monotherapy on body weight loss, despite ZP6590 monotherapy having negligible effect on body weight**
- **Addition of ZP6590 to SEMA therapy after achieving maximal effect of SEMA on weight loss potentiated the effect on weight loss and resulted in weight loss that was equivalent to continuous combination therapy with SEMA and ZP6590 throughout the study**

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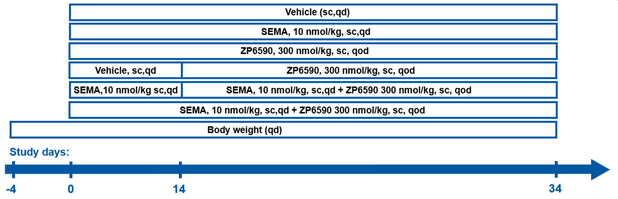
INTRODUCTION

- Current therapies for weight management may be associated with inadequate efficacy and treatment limiting side effects. Consequently, combination therapy leveraging complementary modes of action is warranted to maximize the effect on weight management while maintaining an acceptable safety and tolerability profile.
- Glucose-dependent Insulinotropic Polypeptide (GIP) belongs to incretin family and acts via GIP receptors in the hindbrain to suppress appetite and is a promising candidate for the development of combination therapy for improved weight management.
- ZP6590 is a long-acting GIP analogue with a predicted half-life supporting once-weekly dosing in humans.
- SEMA is a once-weekly GLP-1 agonist approved for chronic weight management for adults with obesity.

METHODS

- DIO mice were treated for 2 weeks by sc injection with either vehicle (qd), ZP6590 (300 nmol/kg, qod), SEMA, 10 nmol/kg, qd) or combination of SEMA + ZP6590 (10 nmol/kg, qd and 300 nmol/kg, qod, respectively).
- From day 14 to day 34, mice dosed with vehicle were continued on vehicle or switched to ZP6590, mice dosed with ZP6590 continued ZP6590 treatment, mice dosed with SEMA either continued SEMA treatment or were switched to the combination therapy of SEMA + ZP6590.
- Mice dosed with combination therapy of SEMA + ZP6590 continued the combination therapy.
- The anti-obesity effects were assessed by measurement of body weight

STUDY DESIGN



RESULTS

Differences in pharmacokinetics of ZP6590 and SEMA when dosed sc to mice supporting the different dosing regimens - QD for SEMA and QOD for ZP6590

Table 1: Pharmacokinetics of ZP6590 and SEMA in mice (n=3).

	SC parameters	
	$T_{½}$, (h, Mean)	T_{max} (h, Median)
ZP6590	16	12
SEMA	8	4

RESULTS

Combination treatment with ZP6590 potentiates the effect of SEMA therapy on body weight loss in DIO mice. Addition of ZP6590 treatment to SEMA therapy on day 14, when maximal effect of SEMA therapy on body weight loss was achieved potentiated the effect on body weight reduction to a similar as combination therapy throughout the study. ZP6590 alone did not result in significant body weight reduction

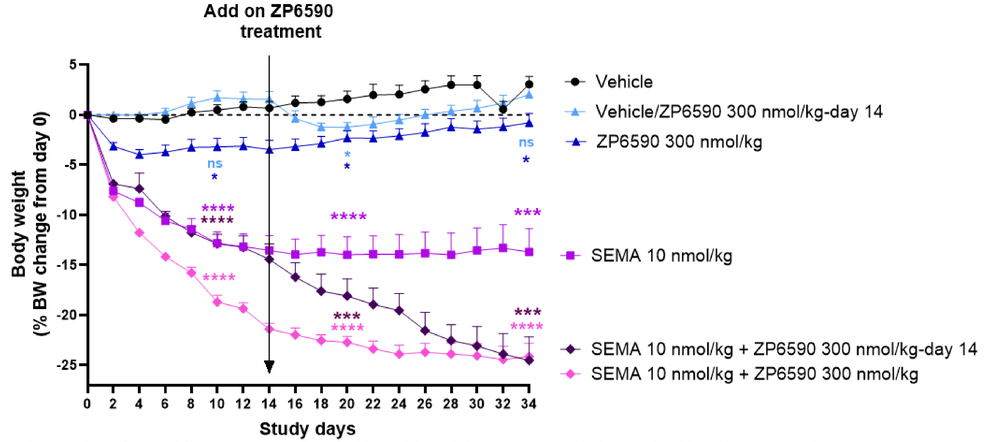


Figure 1: Body weight change from day 0 (%) Data are mean values with SEM (n=5-9/group). Data were compared by 2-way ANOVA followed by Dunnett's multiple comparison test. Significant difference vs. vehicle group, **p<0.01, ***p<0.001, ****p<0.0001, ns=not significant. For clarity stats are shown for selected days (Study day 10, 20 and 34)

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