Safety, tolerability, and clinical effects of ZP8396, an amylin analog: Multiple ascending dose trial

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INTRODUCTION

ZP8396 is a novel amylin analog designed for once-weekly dosing that has demonstrated the potential to reduce body weight and improve glycemia in animal models of obesity and diabetes.

Single doses of up to 2.4 mg of ZP8396 were previously assessed in healthy subjects leading to dose-dependent and consistent reductions in body weight, supporting its potential as a treatment for obesity.

STUDY OBJECTIVE

A multiple ascending dose (MAD) trial to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ZP8396.

METHODS

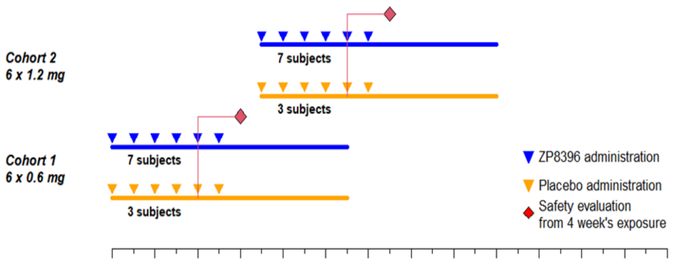
The randomized, double-blind, placebo-controlled trial assessed safety, PK, and PD of six once-weekly subcutaneous injections of ZP8396 in healthy lean and overweight subjects. A total of 20 subjects (mean body weight of 82 kg and BMI of 25.4 kg/m^2) were randomized to ZP8396 or placebo (7:3) within two dose cohorts of 0.6 mg and 1.2 mg.

TRIAL DESIGN

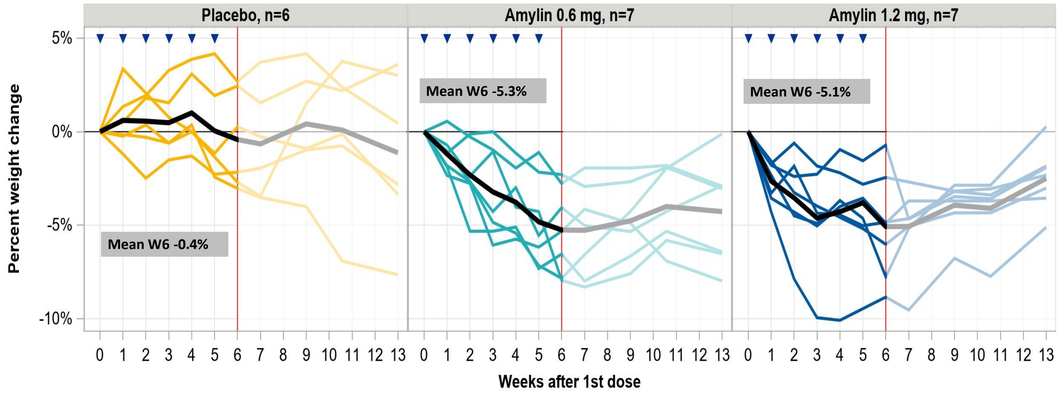
Multiple Ascending Dose Trial Part 1

2 dose cohorts of 6 once-weekly administrations of ZP8396 or placebo

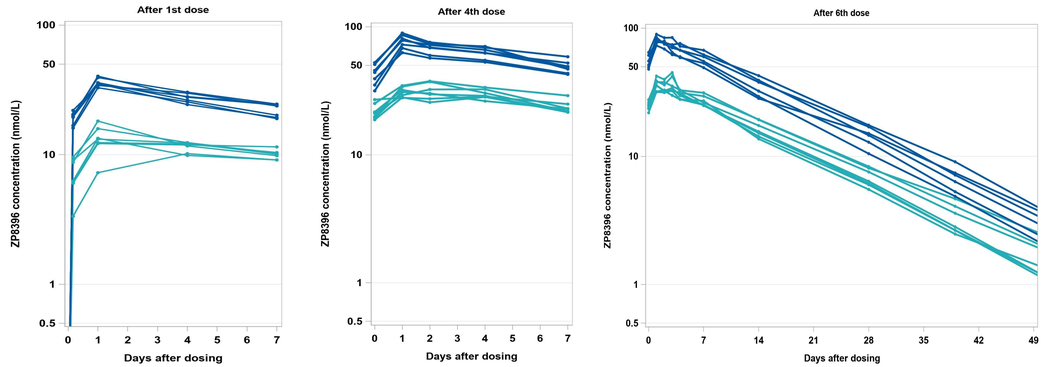
8-week follow-up period after 6th dose



WEIGHT LOSS (%) - MEAN & INDIVIDUAL PROFILES



PHARMACOKINETICS



The half-life was approx. 10 days, with the accumulation factor for C_{max} and AUC_{tau} from 1st to 6th dose being 2.5-fold

TREATMENT EMERGENT ADVERSE EVENTS (TEAEs)

No. of subjects (events)	Placebo n = 6	0.6 mg n = 7	1.2 mg n = 7
Total AEs	5 (28)	6 (23)	7 (29)
Mild	5 (24)	6 (23)	7 (27)
Moderate	3 (4)	0	1 (2)
Severe	0	0	0
Serious	0	0	0
Metabolism and nutrition disorders	1 (1)	6 (9)	6 (8)
Gastrointestinal disorders	3 (7)	2 (6)	5 (9)

RESULTS

- Mean body weight decreased by 0.4%, 5.3% and 5.1% from baseline following six once-weekly doses of placebo, 0.6 mg and 1.2 mg of ZP8396, respectively.
- ZP8396 was well tolerated, with no serious or severe adverse events (AEs) and no withdrawals.
- The most frequent related AEs were decreased appetite, early satiety, food aversion and nausea, all were mild, transient and most had an onset within 2 days of the first dose. Nausea occurred in three subjects treated with ZP8396, with one also reporting vomiting, no other subjects reported vomiting.
- No injection site reactions were reported, and no subjects developed anti-drug antibodies.
- 90% of steady state was reached after 4 weeks.

CONCLUSIONS

- The first part of this MAD trial shows that ZP8396 is safe, well tolerated and induces meaningful reductions in body weight.
- The magnitude of weight loss is comparable to that observed with other weight management therapies recently approved or in development over a treatment duration of six weeks.
- The second part of this MAD trial with longer treatment duration and dose up-titration is exploring doses above 1.2 mg to further assess the clinical potential of ZP8396 for the management of overweight and obesity.