# Novel once-weekly amylin analog petrelintide (ZP8396) is well tolerated with improved GI tolerability after multiple dosing

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## Introduction and Background

- Petrelintide (ZP8396) is a novel, s.c. once-weekly amylin analog, in development for weight management.
- Phase 1 trials (Olsen MB et al, 2023[1,2]) investigated safety, pharmacokinetics (PK) and pharmacodynamics (PD) of petrelintide after single (SD) or multiple dosing (MD).

## Objective

- To compare tolerability of doses with similar exposure levels after single (SD) or multiple dosing (MD).

## Methods

- SAD trial: Participants, healthy, lean or overweight (BMI 21-29.9), were randomized to a SD of petrelintide or placebo (6:2) in eight cohorts (seven s.c. cohorts: 0.04 mg, 0.08 mg, 0.16 mg, 0.35 mg, 0.7 mg, 1.4 mg or 2.4 mg, and one i.v. cohort: 0.35 mg).
- MAD trial: Participants, healthy, lean or overweight (BMI 21-29.9), were randomized to petrelintide or placebo (7:3) in two cohorts (0.6 mg or 1.2 mg), for 6 weeks of treatment, with no dose escalation.
- PK at steady state, body weight reduction and adverse events (AEs) from the Gastrointestinal (GI) and Metabolism and Nutrition SOC are compared descriptively between 1.4 mg s.c. SD and 0.6 mg s.c. MD and between 2.4 mg s.c. SD and 1.2 mg s.c. MD, respectively.

References:

1. Olsen MB, Hovelmann U, Griffin J, Knudsen KM, Johansen T, Kendall D, Heise T. Safety, tolerability, and clinical effects of ZP8396, a novel long-acting amylin analog - a single ascending dose trial. *Diabetes* 2023;72(Supplement_1):92-LB.
2. Olsen MB, Hovelmann U, Griffin J, Knudsen KM, Johansen T, Kendall D, Heise T. Safety, tolerability, and clinical effects of ZP8396, a novel amylin analog – multiple ascending dose trial. Poster abstracts. Obesity week 2023. 84:289.

## Results

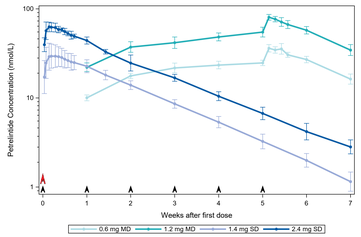
- All AEs were mild to moderate, with no serious or severe AEs, and no treatment discontinuations reported.
- No moderate GI AEs were seen after MD. The most frequently related AEs were decreased appetite, nausea and vomiting. The percentage of participants reporting either decreased appetite and/or early satiety were similar after SD and MD.
- The mean body weight reduction was 3.6% and 4.2% in the SAD cohorts (1.4 and 2.4 mg dosing) and 5.3% and 5.1% in MAD cohorts (0.6 and 1.2 mg dosing), after one or six weeks of dosing, respectively.

| Baseline Characteristics | SAD 8 cohorts (N=64) | MAD 2 cohorts* (N=20) |
|---|---|---|
| Age, years, mean (SD) | 37.8 (8.9) | 31.6 (8.7) |
| Male, n (%) | 64 (100) | 20 (100) |
| Body Weight, kg, mean (SD)<br>Range | 84 (8.1)<br>70 - 112.1 | 81.7 (10)<br>82.1 - 102.8 |
| BMI, kg/m$^2$, mean (SD)<br>Range | 25.6 (2.0)<br>22 - 28.9 | 25.4 (2.1)<br>22.4 - 29.6 |

* Two subjects did not receive the 6th dose

## Pharmacokinetics

Fig 1: SD of 1.4 and 2.4 mg resulted in similar exposures in terms of $C_{max}$ and $AUC_{tau}$ to MD of 0.6 and 1.2 mg at steady state




= single dose day
= multiple dosing days

## Change in body weight

Fig 2: After single dosing (SD)

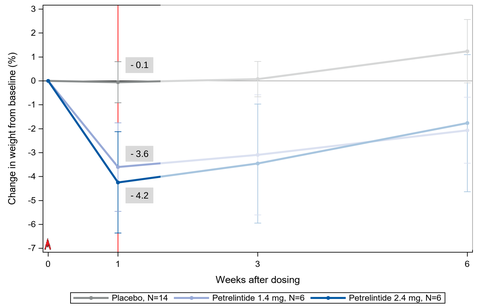
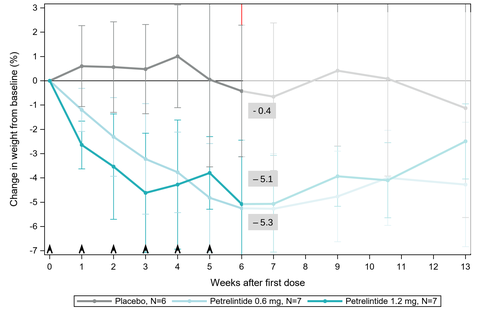



Fig 3: After multiple dosing (MD)




= single dose day
= multiple dosing days

## AEs: Gastrointestinal and metabolism / nutrition disorders

### Most common AEs*

| | SAD trial N(%)E | | | MAD trial N(%)E | | |
|---|---|---|---|---|---|---|
| TEAE summary | Placebo n=14 | 1.40 mg n=6 | 2.40 mg n=6 | Placebo n=6 | 0.6 mg n=7 | 1.2 mg n=7 |
| Gastrointestinal disorders AEs, total | 0 | 5 (83%) 9 | 5 (83%) 12 | 3 (50%) 7 | 2 (29%) 6 | 5 (71%) 9 |
| Nausea | 0 | 4 (67%) 6 | 5 (83%) 7 | 2 (33%) 2 | 1 (14%) 2 | 2 (29%) 2 |
| Abdominal Pain | 0 | 0 | 0 | 1 (17%) 1 | 1 (14%) 1 | 1 (14%) 1 |
| Vomiting | 0 | 1 (17%) 1 | 4 (67%) 5 | 1 (17%) 1 | 1 (14%) 3 | 0 |
| Metabolism and nutrition disorders AEs, total | 0 | 5 (83%) 5 | 6 (100%) 8 | 1 (17%) 1 | 6 (86%) 9 | 6 (86%) 8 |
| Decreased appetite | 0 | 5 (83%) 5 | 6 (100%) 6 | 0 | 5 (71%) 6 | 4 (57%) 5 |
| Early satiety | 0 | 0 | 2 (33%) 2 | 1 (17%) 1 | 2 (29%) 2 | 1 (14%) 1 |
| Food aversion | 0 | 0 | 0 | 0 | 1 (14%) 1 | 2 (29%) 2 |

* Occurring in two or more subjects dosed with petrelintide

### AE severity

| | SAD trial N(%)E | | | MAD trial N(%)E | | |
|---|---|---|---|---|---|---|
| | Placebo n=14 | 1.40 mg n=6 | 2.40 mg n=6 | Placebo n=6 | 0.6 mg n=7 | 1.2 mg n=7 |
| Gastrointestinal disorders AEs, total | 0 | 5 (83%) 9 | 5 (83%) 12 | 3 (50%) 7 | 2 (29%) 6 | 5 (71%) 9 |
| Mild | 0 | 4 (67%) 6 | 2 (33%) 4 | 3 (50%) 6 | 2 (29%) 6 | 5 (71%) 9 |
| Moderate | 0 | 3 (50%) 3 | 4 (67%) 8 | 1 (17%) 1 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 |
| Metabolism and nutrition disorders AEs, total | 0 | 5 (83%) 5 | 6 (100%) 8 | 1 (17%) 1 | 6 (86%) 9 | 6 (86%) 8 |
| Mild | 0 | 4 (67%) 4 | 4 (67%) 6 | 1 (17%) 1 | 6 (86%) 9 | 6 (86%) 8 |
| Moderate | 0 | 1 (17%) 1 | 2 (33%) 2 | 0 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 |

## Conclusions

- Petrelintide was well tolerated, with GI tolerability improving after multiple dosing when exposure is gradually increased.
- AEs of decreased appetite and early satiety were similar after SD and MD.
- Based on these results, higher doses are being explored to assess the potential for weight management.