EFFECTS OF THE NOVEL LONG-ACTING AMYLIN ANALOGUE PETRELINTIDE ON BODY WEIGHT AND WAIST CIRCUMFERENCE BY SEX IN A PHASE 1 TRIAL

ZEALAND PHARMA

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Dan Hesse[1], Minna Brændholt Olsen[1], Jon Griffin[1], Ulrike Hövelmann[2], Stanislava Macura[1], Thue Johansen[1], Berith Fredsted Hagen[1], Helle Frimer-Larsen[1], Tim Heise[2]

[1]Zealand Pharma A/S, Soeborg, Denmark; [2]Profil, Neuss, Germany

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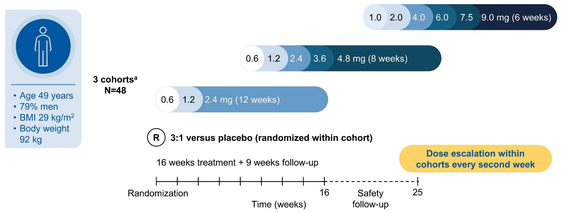
INTRODUCTION AND BACKGROUND

- Petrelintide (ZP8396) is a s.c. once-weekly human amylin analog, in development for weight management.
- Phase 1 trials[1, 2, 3] investigated safety, pharmacokinetics (PK) and pharmacodynamics (PD) of petrelintide after single or multiple dosing.
- Treatment with GLP1-RAs results in greater weight loss in women, whereas this is currently unknown for amylin analogs.

OBJECTIVE

- The phase 1 multiple ascending dose (MAD) trial part 2[3] investigated treatment with once-weekly s.c. petrelintide; effects by sex were explored post hoc and are presented here.

Trial Design: Petrelintide Phase 1b MAD (a randomised, double-blind, placebo-controlled, Phase 1b MAD trial)



[a]Safety evaluation occurred after 4 weeks of treatment at the target dose for each cohort; initiation of the next, higher dose cohort only occurred following safety evaluation for the previous cohort

Sources: 1. ClinicalTrials.gov (NCT05613387), accessed October 2024; 2. Data on file.

References

1. Olsen MB et al. 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 et al. Safety, tolerability, and clinical effects of ZP8396, a novel amylin analog – multiple ascending dose trial. Poster abstracts. Obesity week 2023. 84:289.
3. Heise T et al, Safety, tolerability, and clinical effects of petrelintide (ZP8396), a long acting amylin analog. Oral abstracts. Obesity (Silver Spring). 2024; 32 (Suppl 1) 5-54.

METHODS

- Healthy participants (N=48) with overweight/obesity (79% men, median age 49 yrs, BMI 29 kg/m^2, body weight (BW) 92 kg, waist circumference (WC) 102 cm) were randomized 3:1 to petrelintide or placebo within three cohorts and treated for 16 weeks.
- After dose escalation, target doses of 2.4, 4.8 and 9.0 mg were administered for 12, 8 and 6 weeks, respectively. For dose levels >4.8 mg, a dose included 2 or 3 injections.
- Adverse events (AEs), BW and WC by sex were analyzed post-hoc across treatment groups. The pooled placebo group included 2 women.

Fig 1: Individual change in weight (%) by sex

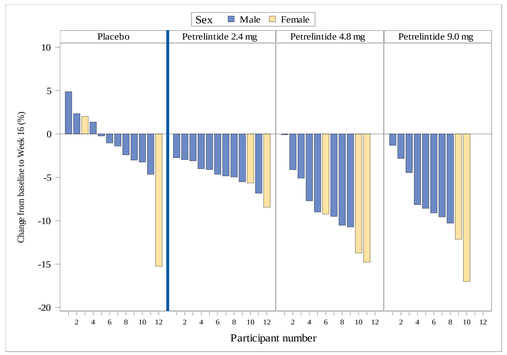


Table 1: Change in BW and WC from baseline to week 16 in petrelintide treated participants (who completed 16 weeks of treatment, total and by sex)

Dose group	2.4 mg (N=12)		4.8 mg (N=11)		9.0 mg (N=10)	
BW reductions	4.8 %		8.6 %		8.3 %	
Mean (min-max)	(2.7-8.4%)		(0.1-14.8%)		(1.3-17.0%)	
WC reductions	5.0 cm		7.2 cm		7.6 cm	
Mean (min-max)	(2-20cm)		(-2-17cm)		(2-18cm)	
Per sex per dose group	**2. 4 mg**		**4.8 mg**		**9.0 mg**	
	Men (N=10)	**Women (N=2)**	**Men (N=8)**	**Women (N=3)**	**Men (N=8)**	**Women (N=2)**
BW reduction	4.4%	7.0%	7.1%	12.6%	6.8%	14.6%
Mean (min-max)	(2.7-6.8%)	(5.6-8.4%)	(0.1-10.7%)	(9.2-14.8%)	(1.3-10.3%)	(12.1-17.0%)
WC reduction	3.5 cm	12.5 cm	5.0 cm	13.0 cm	5.9 cm	14.5 cm
Mean (min-max)	(2-6 cm)	(5-20 cm)	(-2-11 cm)	(8-17 cm)	(2-9 cm)	(11-18 cm)

BW=body weight; WC=waist circumference, N=number of participants

RESULTS

- At 16 weeks, mean BW decreased by 4.8, 8.6 and 8.3% (Figure 1) and WC by 5.0, 7.2 and 7.6 cm with the three petrelintide doses versus 1.7% (BW) and 1.9 cm (WC) for pooled placebo.
- A consistently greater treatment response was observed in women across the three petrelintide treated cohorts (Table 1).
- No clear pattern of differences between men and women were observed for GI adverse events or any other adverse events (Table 2). For additional TEAEs use the QR code.

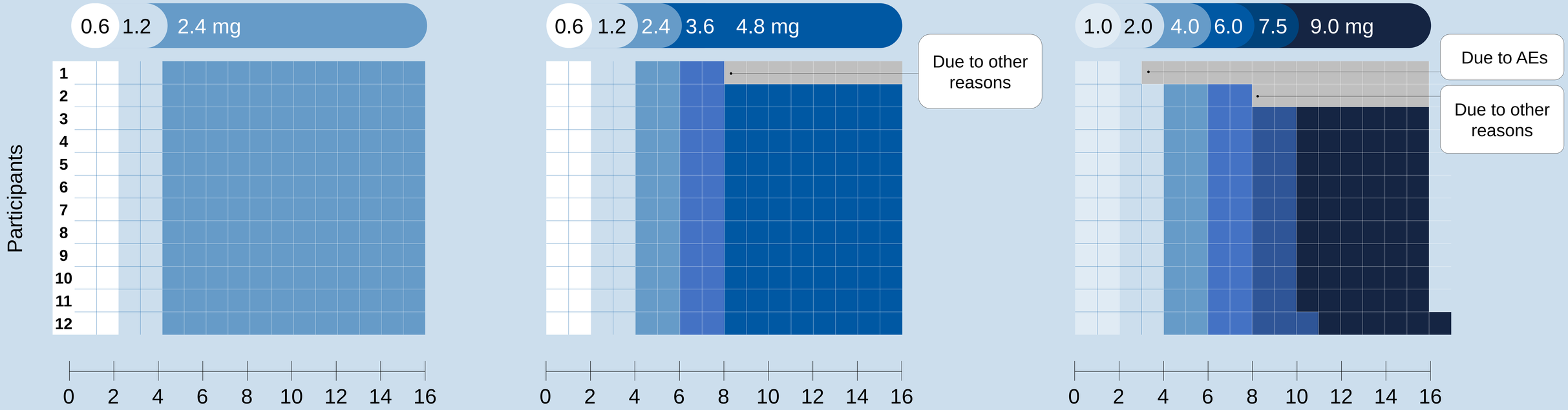
Table 2: Adverse events (AEs) reported for men and women: selected SOCs and PTs (pooled petrelintide and pooled placebo)

	Petrelintide		Placebo	
System Organ Class (SOC) Body system	**Men (N=28) N (%) E**	**Women (N=8) N (%) E**	**Men (N=10) N (%) E**	**Women (N=2) N (%) E**
Gastrointestinal Disorders	16 (57) 31	3 (38) 16	3 (30) 4	2 (100) 7
• Nausea	7 (25) 9	3 (38) 10	0	2 (100) 2
• Vomiting	0 (0)	1 (13) 2	0	0
• Diarrhoea	2 (7) 2	0 (0)	0	0
• Constipation	2 (7) 2	2 (25) 2	0	1 (50) 1
General disorders	15 (54) 40	1 (13) 1	4 (40) 4	1 (50) 2
• Fatigue	9 (32) 10	1 (13) 1	3 (30) 3	1 (50) 1
• Injection site reaction	8 (28) 28	0	1 (10) 1	1 (50) 1
Metabolism / Nutritional disorders	21 (75) 30	6 (75) 7	5 (50) 8	1 (50) 1
• Decreased appetite	18 (64) 23	6 (75) 6	4 (40) 5	1 (50) 1
• Food aversion	1 (4) 1	1 (12) 1	0	0

CONCLUSIONS

Petrelintide treatment resulted in clinically relevant reductions in body weight and waist circumference; women showed greater treatment response, with a retained favorable tolerability profile. A phase 2 program with petrelintide is ongoing.

Treatment completion and compliance with dose escalation within cohorts



- **Three participants discontinued** petrelintide: one due to AEs, two due to other reasons
- One participant in the 9.0 mg arm had **an extra week at 7.5 mg** (due to tolerability)
- The remaining participants followed dose escalation steps within cohorts

Source: Data on file.
AE=adverse event.

TEAEs by System Organ Class (pooled petrelintide and pooled placebo)

	Petrelintide		Placebo	
SOCs	**Men (N=28) N (%) E**	**Women (N=8) N (%) E**	**Men (N=10) N (%) E**	**Women (N=2) N (%) E**
Metabolism / Nutrition disorders	21 (75) 30	6 (75) 7	5 (50) 8	1 (50) 1
Gastrointestinal Disorders	16 (57) 31	3 (38) 16	3 (30) 4	2 (100) 7
Nervous system disorders	11 (39) 22	3 (38) 8	3 (30) 5	2 (100) 5
Respiratory, thoracic and mediastinal disorders	19 (68) 27	3 (38) 4	7 (70) 9	1 (50) 1
General disorders and administration site conditions	15 (54) 40	1 (13) 1	4 (40) 4	1 (50) 2
Injury, poisoning and procedural complications	7 (25) 10	1 (13) 1	0	0
Investigations	1 (4) 1	1 (13) 1	0	0
Skin and subcutaneous tissue disorders	2 (7) 2	1 (13) 1	2 (20) 4	1 (50) 1
Cardiac disorders	1 (4) 1	0	0	1 (50) 1
Infections and Infestations	1 (4) 1	0	1 (10) 1	1 (50) 1
Musculoskeletal and connective tissue disorders	6 (21) 7	0	2 (20) 2	1 (50) 1
Psychiatric disorders**	2 (7) 2	0	0	0
Ear and labyrinth disorders	1 (4) 1	0	0	0
Hepatobiliary disorders	1 (4) 1	0	0	0
Renal and urinary disorders	1 (4) 1	0	1 (10) 5	0

**The two AEs within the SOC Psychiatric Disorders were: irritability and loss of libido

Source: Data on file.
E=number of events; N=number of participants; n=number of participants with observation; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

TEAEs by System Organ Class

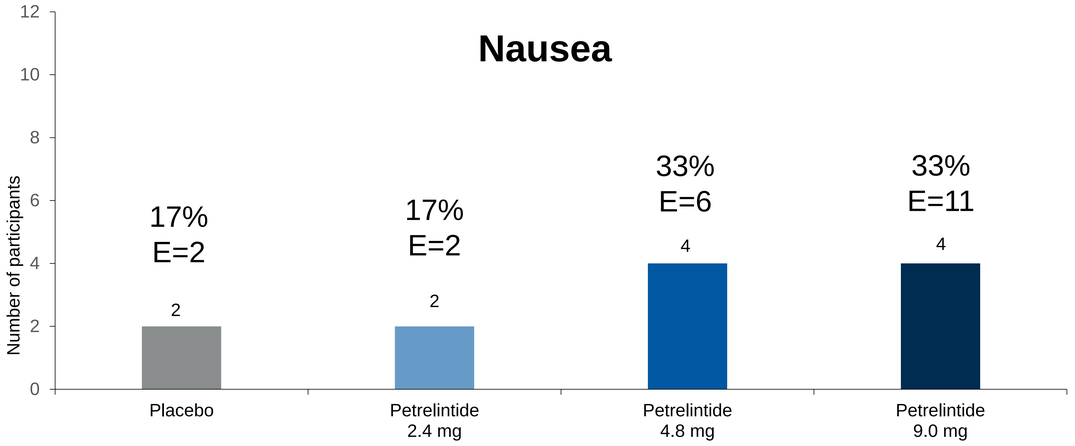
SOCs	Petrelintide 2.4 mg (N=12) N (%) E	Petrelintide 4.8 mg (N=12) N (%) E	Petrelintide 9.0 mg (N=12) N (%) E	Placebo (N=12) N (%) E
Total TEAEs	**12 (100) 58**	**11 (91.7) 63**	**12 (100) 95**	**11 (91.7) 62**
Metabolism and nutrition disorders	10 (83.3) 12	8 (66.7) 12	9 (75.0) 13	6 (50.0) 9
Respiratory, thoracic and mediastinal disorders	8 (66.7) 11	7 (58.3) 12	7 (58.3) 8	8 (66.7) 10
Gastrointestinal disorders	6 (50.0) 9	6 (50.0) 12	7 (58.3) 26	5 (41.7) 11
General disorders and administration site conditions	6 (50.0) 8	2 (16.7) 13	8 (66.7) 20	5 (41.7) 6
Nervous system disorders	4 (33.3) 6	4 (33.3) 7	6 (50.0) 17	5 (41.7) 10
Musculoskeletal and connective tissue disorders	3 (25.0) 4	1 (8.3) 1	2 (16.7) 2	3 (25.0) 3
Injury, poisoning and procedural complications	2 (16.7) 4	3 (25.0) 3	3 (25.0) 4	0
Skin and subcutaneous tissue disorders	1 (8.3) 1	1 (8.3) 1	1 (8.3) 1	3 (25.0) 5
Infections and infestations	0	1 (8.3) 1	0	2 (16.7) 2
Renal and urinary disorders	1 (8.3) 1	0	0	1 (8.3) 5
Cardiac disorders	1 (8.3) 1	0	0	1 (8.3) 1
Investigations	0	0	2 (16.7) 2	0
Psychiatric disorders**	0	1 (8.3) 1	1 (8.3) 1	0
Ear and labyrinth disorders	1 (8.3) 1	0	0	0
Hepatobiliary disorders	0	0	1 (8.3) 1	0

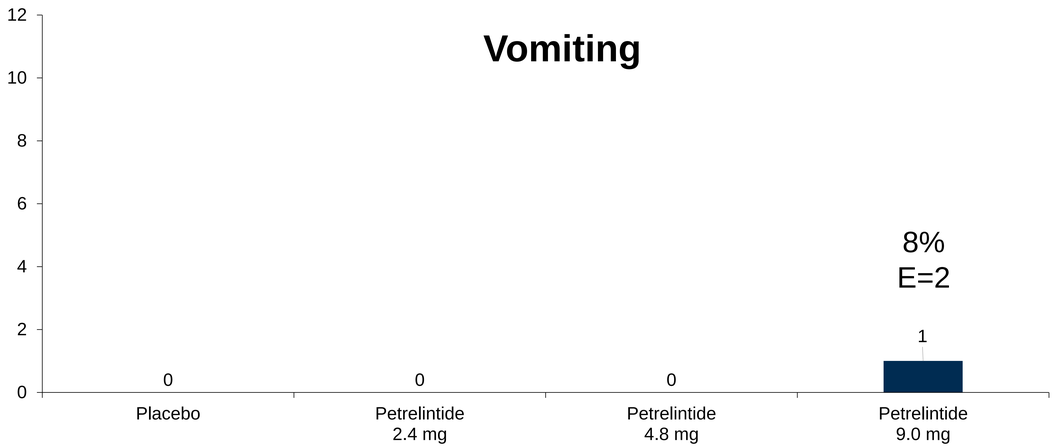
**The two AEs within the SOC Psychiatric Disorders were: irritability and loss of libido

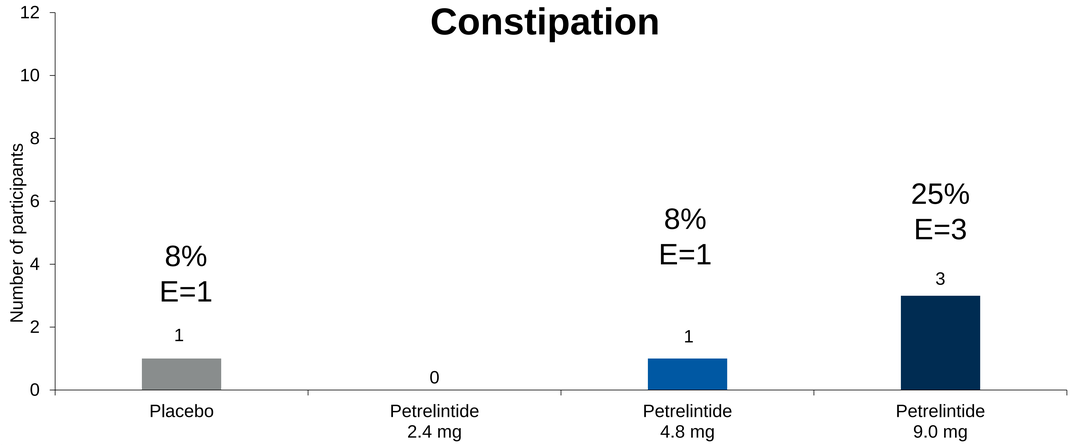
Source: Data on file.
E=number of events; N=number of participants; n=number of participants with observation; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

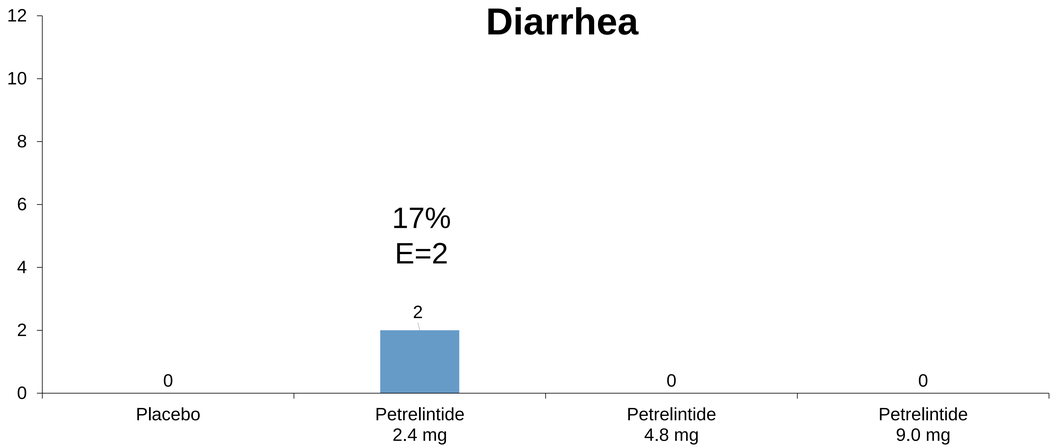
Selected Gastrointestinal TEAEs

All GI TEAEs were mild, except for one event of moderate nausea and one event of moderate vomiting in a single participant









Source: Data on file.
N=12 in each treatment group.
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.