Safety, Tolerability, and Clinical Effects of Petrelintide (ZP8396), A Long-acting Amylin Analog

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On behalf of:

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GLP-1RA-based therapies are efficacious for weight loss, but have been associated with GI tolerability issues[1]

Currently, two once-weekly (OW) GLP-1RA-based therapies are approved for weight management,[2,3] offering mean weight loss of ~15–21%[4,5]

GI adverse events, such as nausea, vomiting, and diarrhea, have been reported with GLP-1RAs, and were a common cause of treatment discontinuation in clinical trials[4,5]

Studies with existing GLP-1RAs have shown discontinuation rates of up to **30%** within **1 month,** and **up to 60–70%** within **12 months** of initiation[6,7]

Amylin is a **pancreatic hormone** involved in **satiety regulation**[8,9]

Amylin analogs have demonstrated **efficacy in metabolic diseases**[10-12] and may represent an **alternative to GLP1-RA-based therapies in obesity**

Sources: 1. Wang et al. Front Endocrinol (Lausanne) 2023;14:1085799; 2. Semaglutide US PI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215256s011lbl.pdf, accessed October 2024; 3. Tirzepatide US PI. Available from: https://pi.lilly.com/us/zepbound-uspi.pdf, accessed October 2024; 4. Wilding et al. N Engl J Med 2021;384(11):989–1002; 5. Jastreboff et al. N Engl J Med 2022;387(3):205–216; 6. Blue Health Intelligence. Real-world trends in GLP-1 treatment persistence and prescribing for weight management. May 2024; 7. Gasoyan et al. Obesity (Silver Spring) 2024;32(3):486–493; 8. Hay et al. Pharmacol Rev 2015;67(3):564–600; 9. Trevaskis et al. Endocrinology. 2008;149(11):5679–5687; 10. Smith et al. Diabetes Care 2008;31(9):1816–1823; 11. Lau et al. Lancet 2021;398(10317):2160–2172; 12. Frias et al. Lancet 2023;402(10403):720–730.
GI=gastrointestinal; GLP-1RA=glucagon-like peptide-1 receptor agonist; OW=once-weekly.

What is petrelintide?

Petrelintide (ZP8396) is a 36-amino-acid acylated peptide, based on the peptide sequence of **human amylin**[1]

- **Long-acting** acylated amylin analog suitable for OW **administration** in humans[1,2]
- **Chemically and physically stable** at neutral pH, **minimizing fibrillation**[3]
- **Potent agonistic effects** on **amylin and calcitonin receptors**[1,4]
- In a **Phase 1 SAD trial,** petrelintide was well tolerated and showed potential to reduce body weight[5]

Sources: 1. Data on file; 2. Brændholt Olsen et al. Poster 92-LB. Presented at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA; 3. Skarbaliene et al. Poster 1406-P. Presented at ADA 82nd Scientific Sessions, June 3–7, 2022, New Orleans, LA; 4. Eriksson et al. Presentation at ObesityWeek, November 1–4, 2022, San Diego, CA; 5. Brændholt Olsen et al. Poster 92-LB. Presented at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA.
SAD=single ascending dose.

Objectives: Petrelintide Phase 1b MAD

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Primary objective

- To evaluate the **safety and tolerability** of petrelintide administered as multiple SC injections in overweight and obese, but otherwise healthy, subjects in order to identify the maximum tolerated dose with the current dosing regimen

Primary endpoint

- Incidence of TEAEs

2

Secondary and exploratory objectives

- To **investigate the PK properties** of petrelintide after multiple up-titrated SC doses
- To **assess the PD response** to SC administration of petrelintide

Secondary and exploratory endpoints

- PK, safety and PD parameters

Source: ClinicalTrials.gov (NCT05613387), accessed October 2024.
MAD=multiple ascending dose; PD=pharmacodynamic; PK=pharmacokinetic; SC=subcutaneous; TEAEs=treatment-emergent adverse events.

Trial design: Petrelintide Phase 1b MAD

A randomized, double-blind, placebo-controlled, Phase 1b, MAD trial of petrelintide[1,2]

- Adults 18–64 years
- Body weight ≥70 kg
- HbA1c <6.5%
- BMI 27.0–39.9 kg/m^2

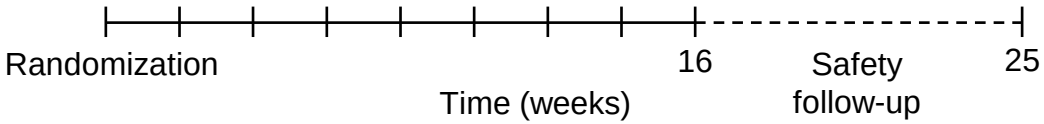
3 cohorts[a]
N=48

Dose escalation within cohorts every second week

- 1.0 | 2.0 | 4.0 | 6.0 | 7.5 | 9.0 mg (6 weeks)
- 0.6 | 1.2 | 2.4 | 3.6 | 4.8 mg (8 weeks)
- 0.6 | 1.2 | 2.4 mg (12 weeks)

R **3:1 versus placebo (randomized within cohort)**

16 weeks treatment + 9 weeks follow-up



[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.[2]
Sources: 1. ClinicalTrials.gov (NCT05613387), accessed October 2024; 2. Data on file.
BMI=body mass index; HbA1c=glycated hemoglobin; MAD=multiple ascending dose; SC=subcutaneous
No lifestyle modifications, such as counselling on diet and exercise.

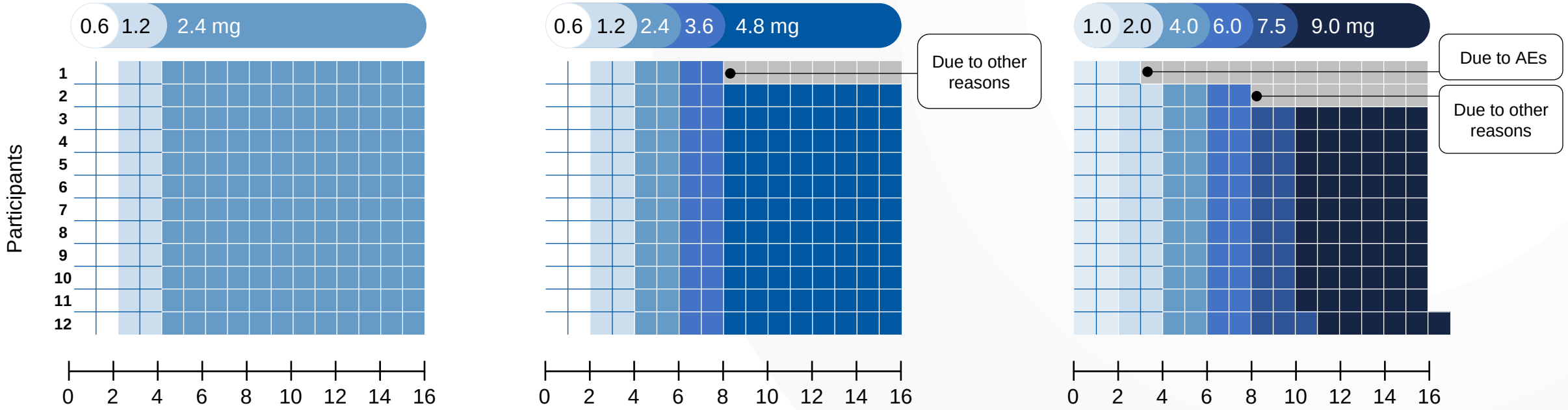
Demographics and clinical characteristics

Petrelintide Phase 1b MAD trial: baseline characteristics[1,2]

	Placebo (N=12)	Petrelintide 2.4 mg (N=12)	Petrelintide 4.8 mg (N=12)	Petrelintide 9.0 mg (N=12)	Total (N=48)
Male sex, n (%)	10 (83)	10 (83)	9 (75)	9 (75)	**38 (79)**
Age (years), mean (min–max)	46 (23–63)	48 (26–57)	42 (26–58)	52 (26–63)	**47 (23–63)**
Body weight (kg), mean (min–max)	93 (75–108)	98 (87–113)	89 (71–108)	88 (72–109)	**92 (71–113)**
BMI (kg/m^2), mean (min–max)	30.3 (28.0–37.1)	30.7 (27.4–35.0)	29.1 (27.2–32.5)	29.4 (27.7–33.0)	**29.9 (27.2–37.1)**

Sources: 1. Zealand Pharma. Press release 20 June 2024. Available from: https://www.globenewswire.com/news-release/2024/06/20/2901879/0/en/Zealand-Pharma-announces-positive-topline-results-from-the-Phase-1b-16-week-multiple-ascending-dose-clinical-trial-with-long-acting-amylin-analog-petrelintide.html, accessed October 2024; 2. Data on file.
BMI=body mass index; MAD=multiple ascending dose; N=number of participants.

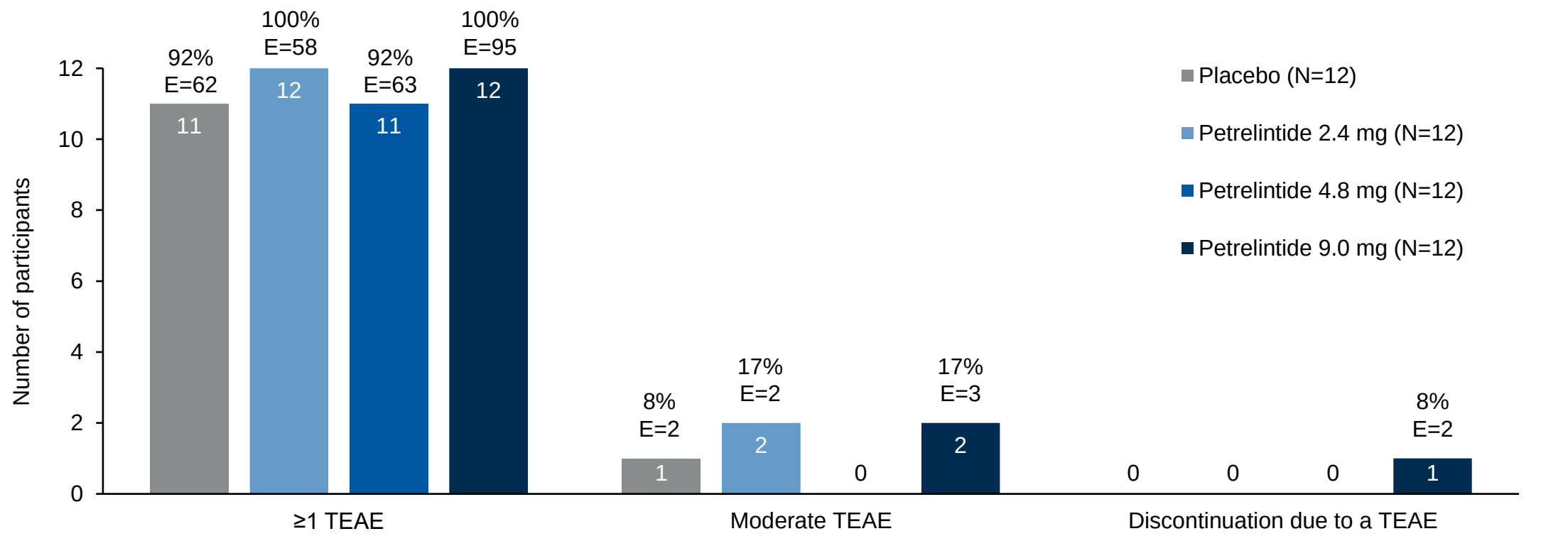
Treatment completion and compliance with dose escalation within cohorts



- **Three participants discontinued** petrelintide: one due to AEs, one to focus on recovery from a cold, and one due to personal 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.

Summary of treatment emergent adverse events (TEAEs)



No serious or severe TEAEs were reported

Source: Data on file.
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.
5 moderate AEs reported by petrelintide exposed participants: nausea, vomiting, nasopharyngitis, acute sinusitis, back pain.

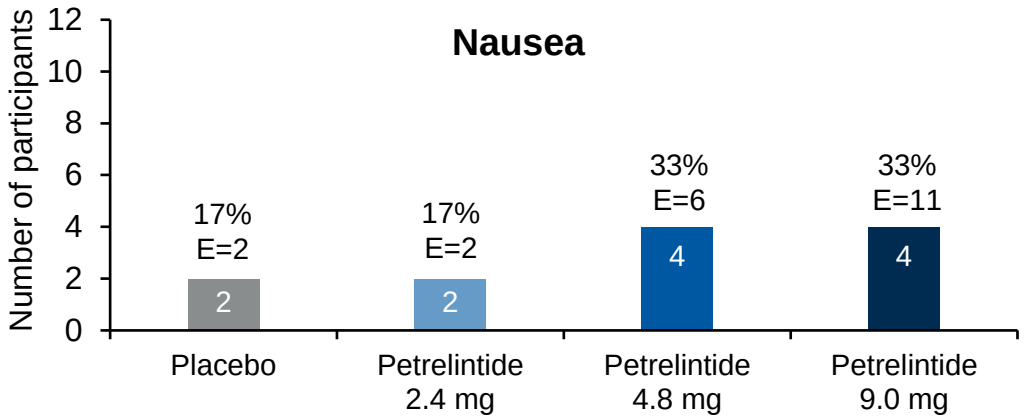
TEAEs by System Organ Class

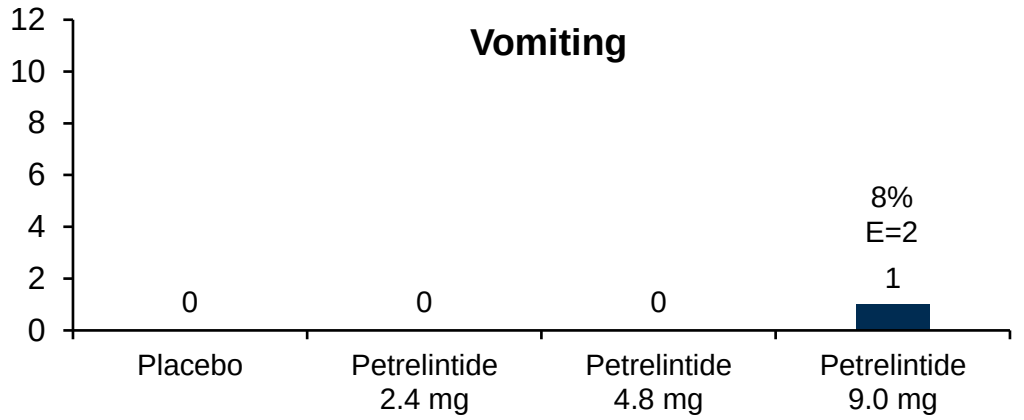
SOC	Placebo n (%) E	Petrelintide 2.4 mg n (%) E	Petrelintide 4.8 mg n (%) E	Petrelintide 9.0 mg n (%) E
Total TEAEs	**11 (91.7) 62**	**12 (100) 58**	**11 (91.7) 63**	**12 (100) 95**
Metabolism and nutrition disorders	6 (50.0) 9	10 (83.3) 12	8 (66.7) 12	9 (75.0) 13
Respiratory, thoracic and mediastinal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

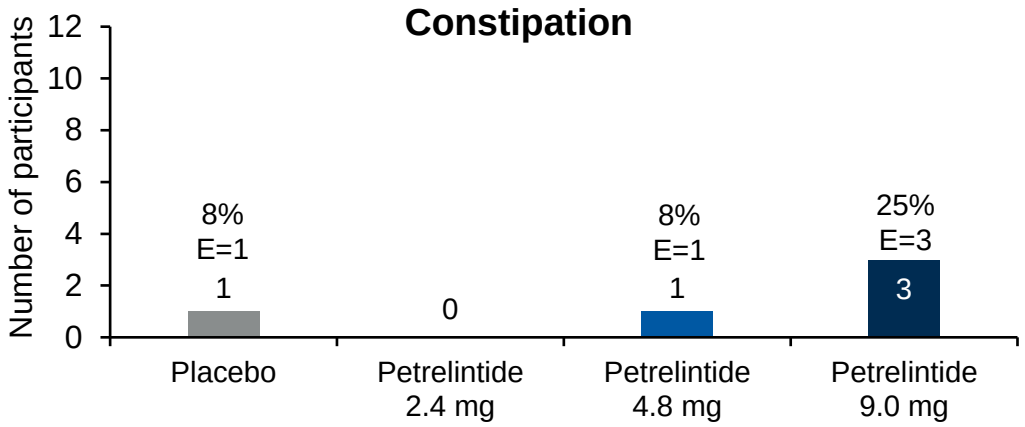
Source: Data on file.
N=12 in each treatment group.
E=number of events; N=number of participants; n=number of participants with observation; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

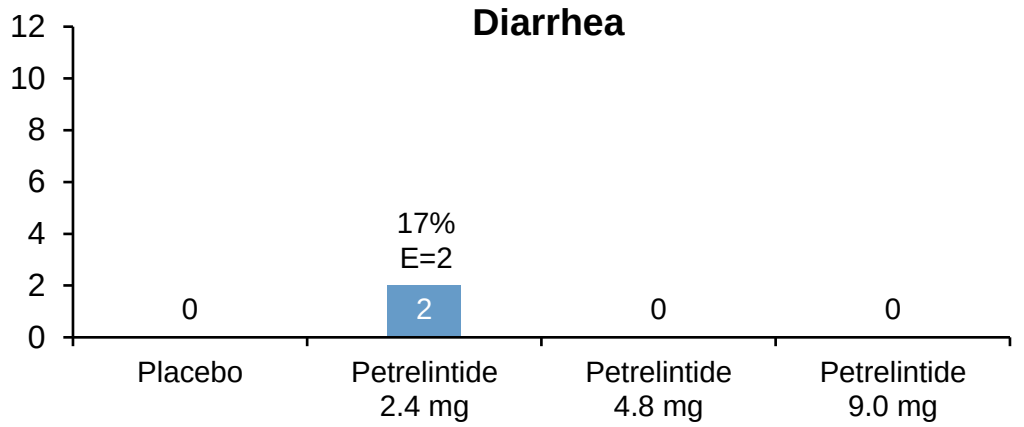
Selected Gastrointestinal TEAEs

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









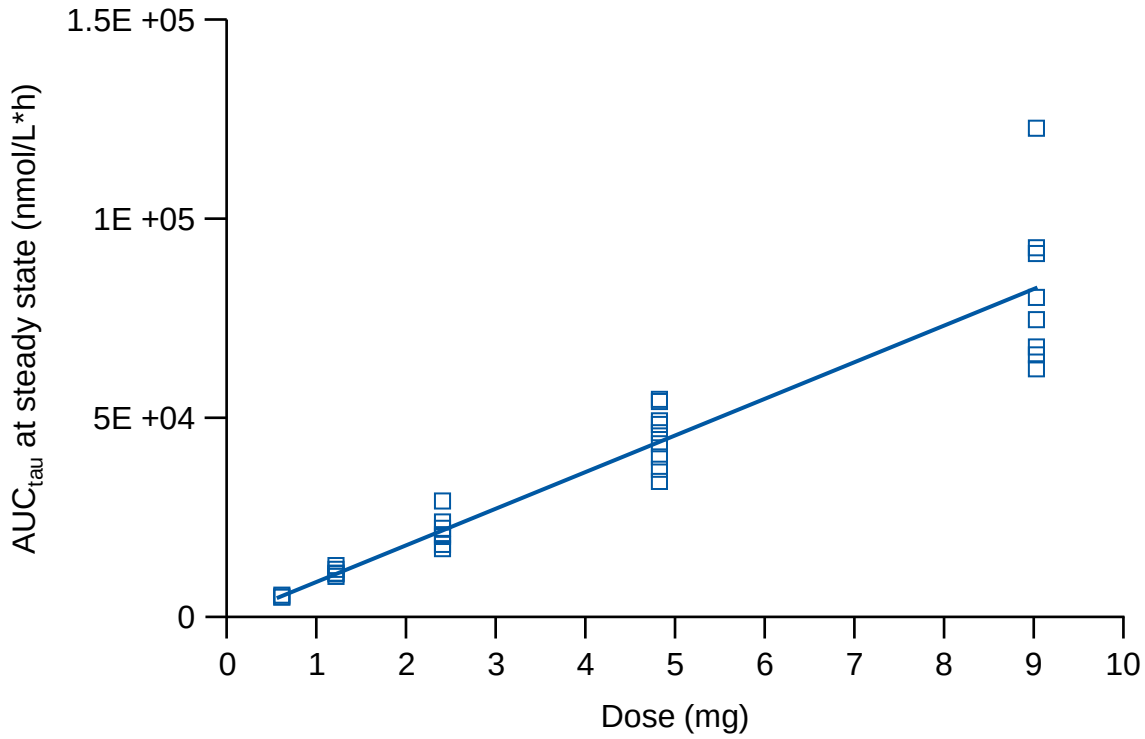
Source: Data on file.
N=12 in each treatment group.
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.

Summary of additional safety parameters

- **No clinically significant findings** for vital signs, ECG, physical examinations, or clinical laboratory assessments
- Mean **pulse rate** decreased for all cohorts compared to placebo and was approximately 5 bpm lower than baseline towards the end of treatment
- Trend for decrease for all cohorts in mean systolic and diastolic **blood pressure** similar to placebo
- No participants developed **antidrug antibodies**
- All injection site reactions were mild, and 2 participants reported the majority of events (63%)

Source: Data on file.
ECG=electrocardiogram.

Summary of pharmacokinetics



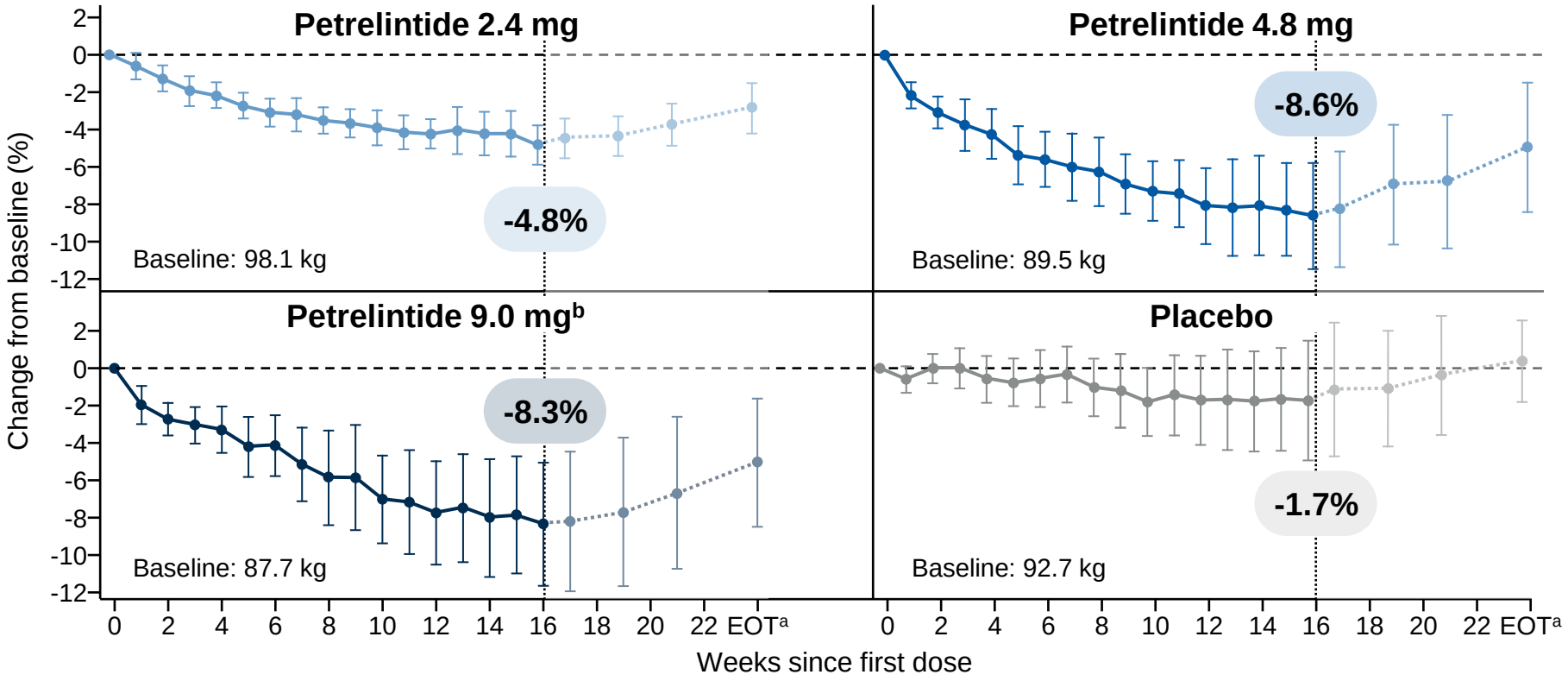
Steady state dose range of 0.6 mg to 9.0 mg

- Petrelintide shows **dose proportional pharmacokinetics** from 0.6 mg to 9.0 mg
  - Both for **C_{max} and AUC_{tau}**
- **T_{max}** was observed at **24 hours**
- **Terminal half-life** of approximately **240 hours (10 days)** was confirmed
- Petrelintide has pharmacokinetic profile suitable for **once-weekly dosing**
- **Bioavailability** following subcutaneous dosing has previously been **determined to be 85%**

Source: Data on file.
AUC=area under the concentration–time curve; AUC_{tau}=area under the concentration–time curve for a dosing interval; C_{max}=peak concentration; MAD=multiple ascending dose; T_{max}=time to peak concentration.

Change in body weight

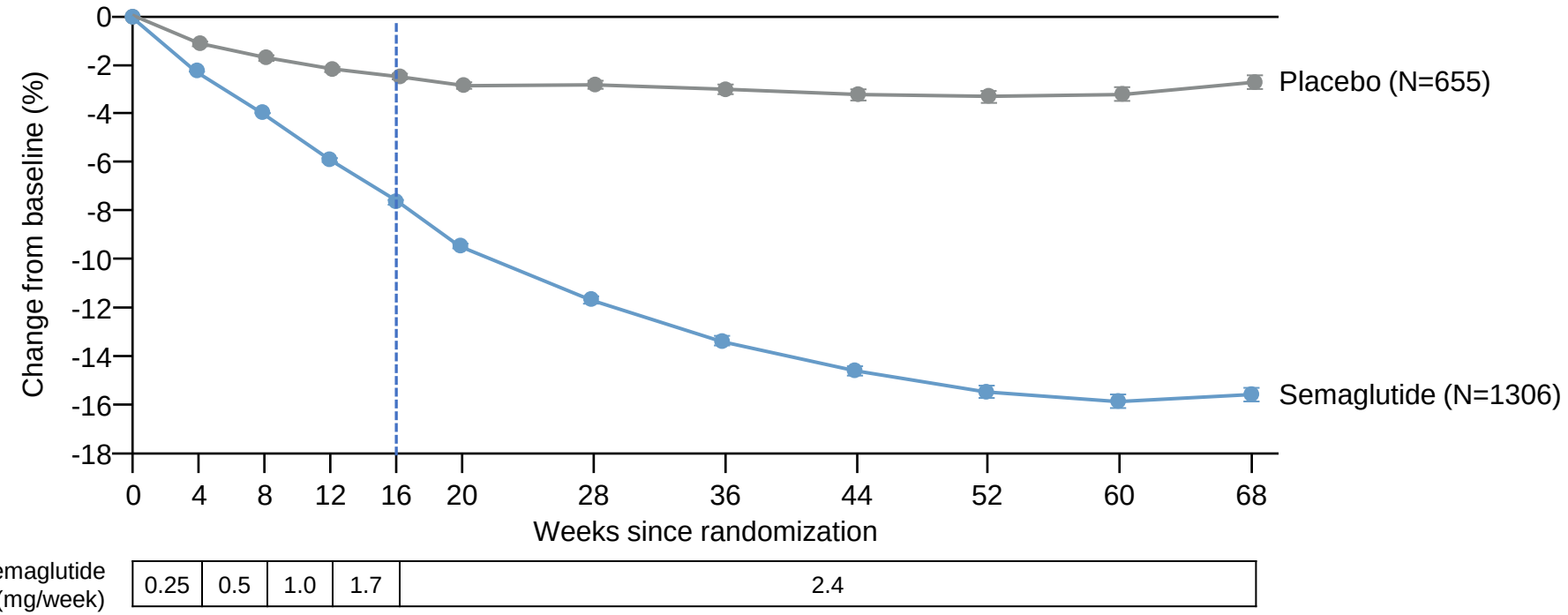
Observed mean (95% CI) percent change from baseline in body weight



[a]EOT includes measurements at the EOT visit, performed at 24 or 25 weeks after dosing, and also performed for participants discontinuing treatment early.
[b]One participant had one extra week at 7.5 mg, and thereby only five weeks on maintenance dose at Week 16. After Week 16, this participant is included with weeks after last dosing.
Source: Data on file.
CI=confidence interval; EOT=end of trial.

STEP 1 – semaglutide SC Phase 3 clinical trial

Mean (95% CI) percent change from baseline in body weight – observed in-trial data



Baseline values **Semaglutide**: 73% female; mean (SD) BMI, 37.8 (6.7) kg/m^2 **Placebo**: 76% female; mean (SD) BMI, 38.0 (6.5) kg/m^2

Source: Figure from N Engl J Med, Wilding et al., Once-Weekly Semaglutide in Adults with Overweight or Obesity, 384(11):989–1002. Copyright © (2021). Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

BMI=body mass index; CI=confidence interval; SC=subcutaneous; SD=standard deviation.

Summary

Safety

- 16 weeks of treatment with petrelintide maintenance doses up to 9.0 mg was **well tolerated** and safe
- The vast majority of TEAEs reported by petrelintide-treated participants were mild; only one participant reported moderate GI AEs
- **Of 36** petrelintide-treated participants, **one participant discontinued due to GI AEs**
- **No antidrug antibodies were developed during the trial**

PK

- Petrelintide had dose proportionality from 0.6 mg to 9.0 mg at steady state and is **suitable for once-weekly dosing**

Efficacy

- For all doses tested, petrelintide (2.4 mg, 4.8 mg, and 9.0 mg) showed greater decrease in body weight compared to placebo
- After **16 weeks of treatment**, mean **weight loss was up to 8.6% with petrelintide** vs 1.7% with placebo

Source: Data on file.
AE=adverse event; GI=gastrointestinal; PK=pharmacokinetics; TEAE=treatment-emergent adverse event.

Overall conclusions

This Phase 1 trial demonstrated excellent **tolerability** of petrelintide and achievement of **clinically relevant weight loss** after 16 weeks

Petrelintide will be further investigated in a Phase 2 obesity trial

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