Petrelintide, a human amylin analog for the treatment of obesity: efficacy and safety from the Phase 2 trial, ZUPREME-1

W. Timothy Garvey[1], Lisa Connery[2], Maj Dinesen[3], Berith F. Hagen[3], Louise Larsen[3], Dan Hesse[3]
[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]AMR Clinical, Norman, Ok, USA; [3]Zealand Pharma A/S, Soeborg, Denmark

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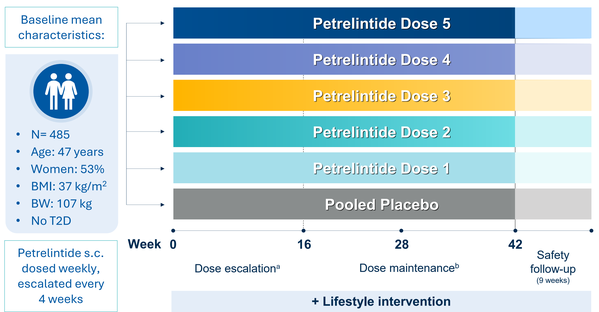
INTRODUCTION AND OBJECTIVE

- Obesity is a heterogeneous, chronic disease for which pharmacotherapy is often required. Despite recent advances in available obesity medicines, treatment persistence outside clinical trials remains low, including due to side effects.[1,2]
- Petrelintide is a human amylin analog with a half-life of approximately 10 days being developed as a once-weekly injectable for long-term obesity pharmacotherapy with a distinct mode of action.[3,4]
- This Phase 2 trial compared the efficacy, safety, and tolerability of various once-weekly doses of petrelintide versus placebo, as an adjunct to lifestyle changes, in people with obesity or overweight with complications.[5]

Trial design

Randomized, double-blind, placebo-controlled, parallel-group, 10-arm, multicenter, multinational, dose-finding trial



[a] Dose escalation ranged from 4-16 weeks
b Volume matched placebo - Participants and Investigators were blinded to treatment allocation but not to the IMP dose.
BMI, body mass index; BW, body weight; N, number of participants in the full analysis set;
s.c., subcutaneous; T2D, type 2 diabetes
Data on file.

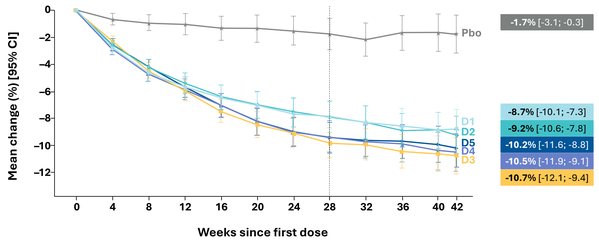
Primary endpoint:
- Percentage change in body weight from baseline to Week 28

Secondary/exploratory endpoints (non-exhaustive):
- Change in body weight at Week 42
- Change in waist circumference at Week 42
- Change in cardiometabolic risk factors at Week 42
- Treatment emergent adverse events

ZUPREME-1: EFFICACY AND SAFETY

Estimated change in body weight

Primary endpoint (W28), secondary endpoint (W42): Efficacy estimand*



*Treatment effect if all participants had remained on IMP and not initiated other anti-obesity treatment. Total treatment discontinuation for any reason at Week 42 was 15.5% (petrelintide range 9.6-18.3%; placebo 24.7%)

CI, confidence interval.

Petrelintide led to mean reductions in body weight from baseline to Week 42 of up to 10.7% vs 1.7% for placebo (efficacy estimand; p<0.001).

- In total, 485 adults were randomized and dosed (53% female; mean age: 47 years, BMI: 36.7 kg/m^2; body weight: 107.1 kg).
- The target dose was reached by 88-98% of participants on petrelintide. At Week 28, all 5 doses of petrelintide reached significantly greater weight loss, compared to placebo.
- Most (>75%) gastrointestinal (GI) AEs were mild. Nausea was the most common GI AE, reported for 19.6% of participants on petrelintide vs 6.2% on placebo. Refer to Selected adverse events and Selected GI AEs tables for details on GI AEs.

Selected adverse events (AE)*

Preferred Term		Petrelintide D1 (N=79)	Petrelintide D2 (N=81)	Petrelintide D3 (N=83)	Petrelintide D4 (N=79)	Petrelintide D5 (N=82)	Petrelintide Pooled (N=404)	Placebo Pooled (N=81)
Nausea	n (%)	15 (19.0)	10 (12.3)	19 (22.9)	12 (15.2)	23 (28.0)	79 (19.6)	5 (6.2)
Fatigue	n (%)	2 (2.5)	7 (8.6)	7 (8.4)	7 (8.9)	8 (9.8)	31 (7.7)	4 (4.9)
Diarrhea	n (%)	3 (3.8)	9 (11.1)	7 (8.4)	7 (8.9)	4 (4.9)	30 (7.4)	6 (7.4)
Injection site reactions[a]	n (%)	5 (6.3)	2 (2.5)	6 (7.2)	7 (8.9)	9 (11.0)	29 (7.2)	5 (6.2)
Constipation	n (%)	3 (3.8)	3 (3.7)	5 (6.0)	10 (12.7)	7 (8.5)	28 (6.9)	3 (3.7)
Headache	n (%)	3 (3.8)	0	6 (7.2)	4 (5.1)	7 (8.5)	20 (5.0)	3 (3.7)
Alopecia	n (%)	0	3 (3.7)	4 (4.8)	8 (10.1)	4 (4.9)	19 (4.7)	1 (1.2)
Abdominal pain[b]	n (%)	2 (2.5)	2 (2.5)	2 (2.4)	4 (5.1)	6 (7.3)	16 (4.0)	3 (3.7)
Decreased appetite	n (%)	3 (3.8)	0	5 (6.0)	2 (2.5)	2 (2.4)	12 (3.0)	0
Vomiting	n (%)	3 (3.8)	0	0	2 (2.5)	7 (8.5)	12 (3.0)	5 (6.2)

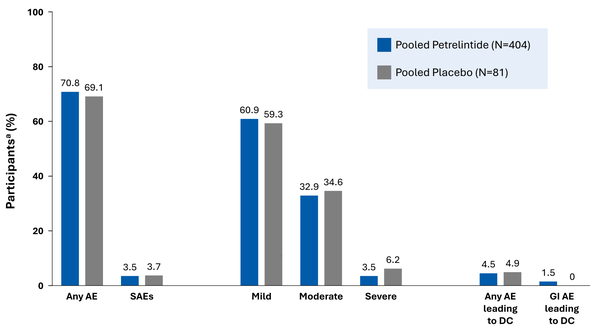
[a] Pool of multiple PTs: Injection site bruising, Injection site discoloration, Injection site erythema, Injection site irritation, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction

[b] Pool of multiple PTs: Abdominal pain, Abdominal pain upper, Abdominal pain lower

*The following PTs were reported by >5% but omitted from the table, as most events are not judged to be related to IMP: Vitamin D deficiency, Upper respiratory tract infection, Urinary tract infection, COVID-19.

N, number of participants in the analysis set; n, number of participants with at least one AE; %, percent of participants reporting at least one AE; PT, preferred term.

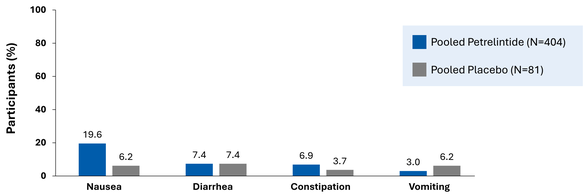
AE overview



[a] Participants reporting at least one AE.

Selected GI AEs

Most GI AEs with petrelintide were mild (77%)



- Only 1.5% of participants discontinued petrelintide due to GI AEs, and there were no unexpected safety findings.
- Petrelintide was associated with improvements in key cardiovascular risk factors. Reductions from baseline ranged from 7.9 to 10.8 cm for waist circumference (vs 4.3 cm with placebo), 17% to 41% for hsCRP (vs 6% with placebo), and 12% to 21% for triglycerides (vs 9% with placebo).

Summary
- In this Phase 2 dose finding trial, petrelintide demonstrated statistically significant and clinically meaningful weight reduction across all dose cohorts at both Week 28 and through Week 42 in a gender-balanced population
- Treatment with petrelintide was associated with improvements in key cardiovascular risk factors
- Petrelintide treatment was well tolerated with rates of GI AEs and SAEs generally similar to placebo

Conclusions
- These findings support the potential of petrelintide as an effective and well-tolerated obesity medication with a distinct mechanism of action
- These properties offer the opportunity for petrelintide (and amylin-based therapies) to improve longer-term medication persistence
- Petrelintide, a novel amylin analog can potentially play an important role in the future of obesity pharmacotherapy – and Phase 3 studies are scheduled to initiate in second half of 2026

AE, adverse event; DC, discontinuation; GI, gastrointestinal; hsCRP, high-sensitivity C-reactive protein; IMP, investigational medicinal product; SAE, serious adverse event; W, Week.

References: 1. Rodriguez PJ, et al. JAMA Netw Open. 2025. 2. Gasoyan H, et al. Obesity. 2024;32:486-493. 3. Olsen MB, et al. ADA 2023; Poster 92-LB. 4. Munch HF, et al. J Med Chem. 2025;68:23925-23940. 5. Garvey WT, et al. ADA 2026; ePoster Theater, Board 3083.

ePoster Theater: 3083-LB

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Hoffmann-La Roche Ltd. and Zealand Pharma A/S entered into an exclusive collaboration and licensing agreement to co-develop and co-commercialize petrelintide for people living with overweight and obesity.

W. Timothy Garvey, MD
Disclosures

Advisory Boards: Consultant on advisory boards for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pfizer, Fractyl Health, Zealand Pharma, Genentech/Roche, Terns Pharmaceuticals, Neurocrine Biosciences, Keros Therapeutics, Gan & Lee, Corcept Therapeutics, Graviton Bioscience, AbbVie Inc., Madrigal Pharmaceuticals, i2o Therapeutics, and Regeneron Pharmaceuticals.

Clinical Trials: Site principal investigator for multi-centered clinical trials sponsored by his university and funded by Novo Nordisk, Eli Lilly, Zealand Pharma, Genentech/Roche, TERNS Pharmaceuticals, Kailera Pharmaceuticals, Structure Therapeutics, Alveus Therapeutics, Pfizer, and Viking Therapeutics.

Background

- Obesity is a heterogeneous chronic disease for which pharmacotherapy is often required
- Despite recent advances in available obesity medicines, treatment persistence outside clinical trials remains low for several reasons, including side effects[1,2]
- Petrelintide, a human amylin analog (T½ 10 days), is being developed as a weekly injectable for long term obesity pharmacotherapy with a distinct mode of action
- The objective of this Phase 2 trial was to compare the efficacy, safety, and tolerability of various doses of petrelintide vs placebo[a], in people with obesity or overweight with complications[b]

[a] as an adjunct to lifestyle changes
[b] At least one of the following comorbidities: hypertension or dyslipidemia, treated or untreated, at the investigator's discretion
1. Rodriguez et al JAMA 2025. 2. Gasoyan H et al. Obesity. 2023:32(3):486-493

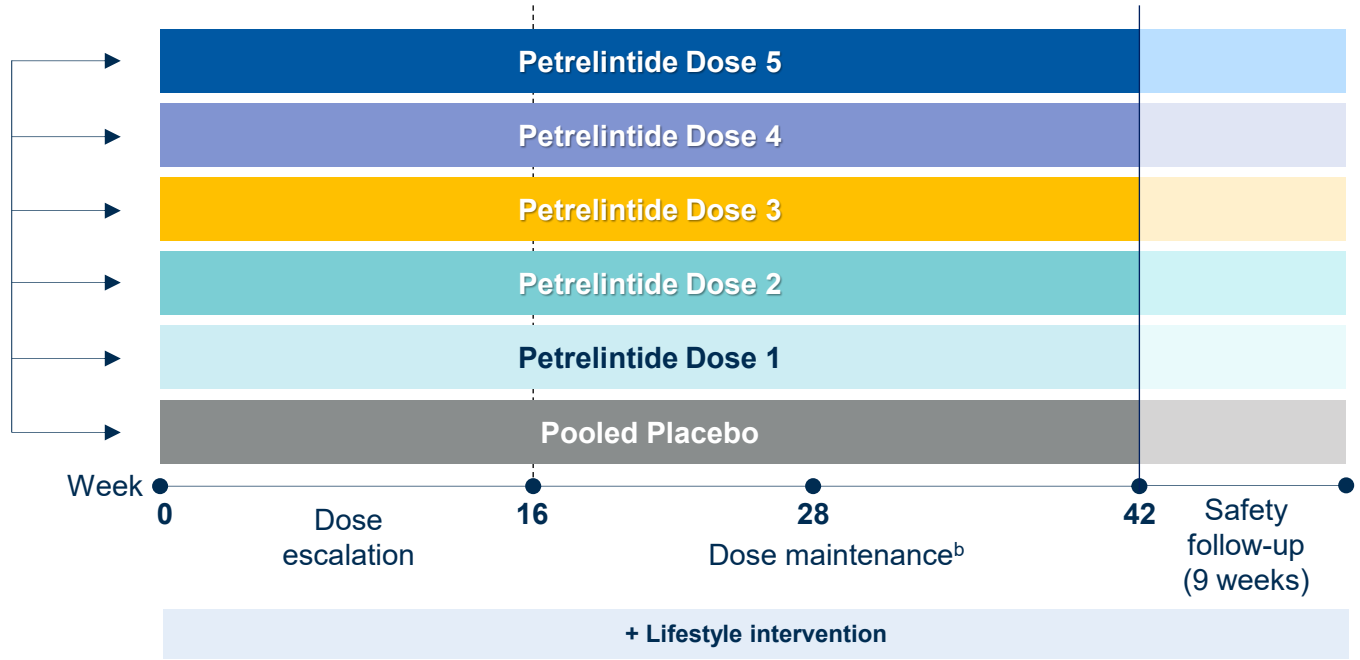
ZUPREME 1 trial design

Randomized, double-blind, placebo-controlled, parallel-group, 10-arm, multicenter, multinational, dose-finding trial

Mean baseline characteristics:

- N= 485
- Age: 47 years
- Women: 53%
- BMI: 37 kg/m^2
- BW: 107 kg
- No T2D

Petrelintide s.c. dosed weekly, escalated every 4 weeks[a]



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b Volume matched placebo - Participants and Investigators were blinded to treatment allocation but not to the IMP dose.
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s.c., subcutaneous; T2D, type 2 diabetes
Data on file.

Primary endpoint:

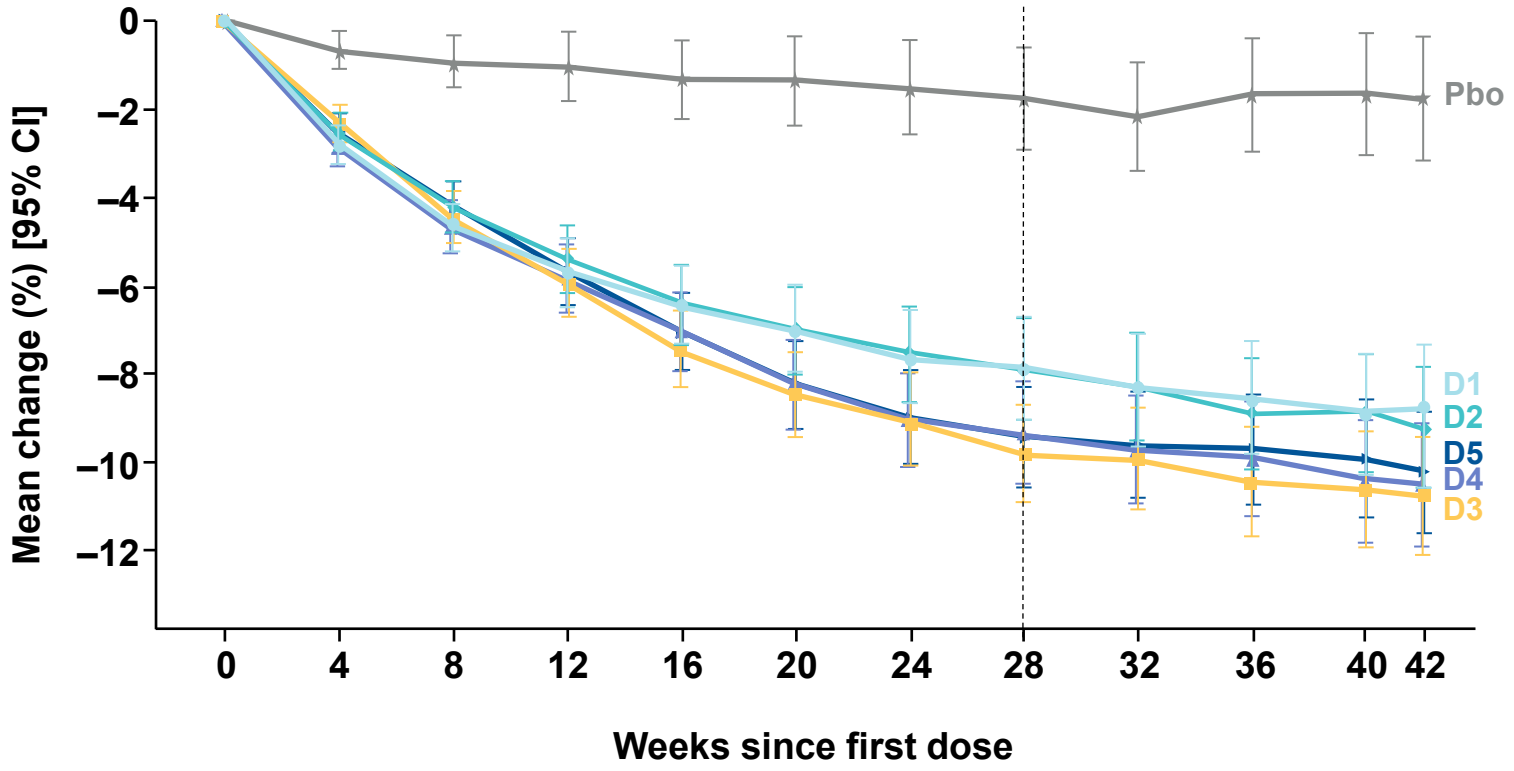
- Percentage change in body weight from baseline to Week 28

Secondary/exploratory endpoints (non-exhaustive):

- Change in body weight at Week 42
- Change in waist circumference at Week 42
- Change in cardiovascular risk factors at Week 42
- Treatment emergent adverse events

Estimated change in body weight

Primary endpoint (W28), secondary endpoint (W42): Efficacy estimand*



Dose	W42 [95% CI]
Pooled Placebo N=81	**-1.7%** [-3.1; -0.3]
Dose 1 N=79	**-8.7%** [-10.1; -7.3]
Dose 2 N=81	**-9.2%** [-10.6; -7.8]
Dose 3 N=83	**-10.7%** [-12.1; -9.4]
Dose 4 N=79	**-10.5%** [-11.9; -9.1]
Dose 5 N=82	**-10.2%** [-11.6; -8.8]

*Treatment effect if all participants had remained on investigational medicinal product (IMP) and not initiated other anti-obesity treatment. Total treatment discontinuation for any reason at Week 42 was 15.5% (petrelintide range 9.6-18.3%; placebo 24.7%)
CI, confidence interval; N, number of participants in the full analysis set.
Data on file.

Adverse events – most common PTs (>5% participants)

Preferred Term (PT)		Petrelintide D1 (N=79)	Petrelintide D2 (N=81)	Petrelintide D3 (N=83)	Petrelintide D4 (N=79)	Petrelintide D5 (N=82)	Petrelintide Pooled (N=404)	Placebo Pooled (N=81)
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Injection site reactions[a]	n (%)	5 (6.3)	2 (2.5)	6 (7.2)	7 (8.9)	9 (11.0)	29 (7.2)	5 (6.2)
Constipation	n (%)	3 (3.8)	3 (3.7)	5 (6.0)	10 (12.7)	7 (8.5)	28 (6.9)	3 (3.7)
Vitamin D deficiency	n (%)	6 (7.6)	8 (9.9)	7 (8.4)	2 (2.5)	5 (6.1)	28 (6.9)	7 (8.6)
Headache	n (%)	3 (3.8)	0	6 (7.2)	4 (5.1)	7 (8.5)	20 (5.0)	3 (3.7)
Alopecia	n (%)	0	3 (3.7)	4 (4.8)	8 (10.1)	4 (4.9)	19 (4.7)	1 (1.2)
Upper respiratory tract infection	n (%)	6 (7.6)	4 (4.9)	3 (3.6)	2 (2.5)	2 (2.4)	17 (4.2)	7 (8.6)
Urinary tract infection	n (%)	1 (1.3)	6 (7.4)	3 (3.6)	3 (3.8)	3 (3.7)	16 (4.0)	2 (2.5)
Abdominal pain[b]	n (%)	2 (2.5)	2 (2.5)	2 (2.4)	4 (5.1)	6 (7.3)	16 (4.0)	3 (3.7)
Decreased appetite	n (%)	3 (3.8)	0	5 (6.0)	2 (2.5)	2 (2.4)	12 (3.0)	0
Vomiting	n (%)	3 (3.8)	0	0	2 (2.5)	7 (8.5)	12 (3.0)	5 (6.2)
COVID-19	n (%)	4 (5.1)	3 (3.7)	0	1 (1.3)	0	8 (2.0)	1 (1.2)

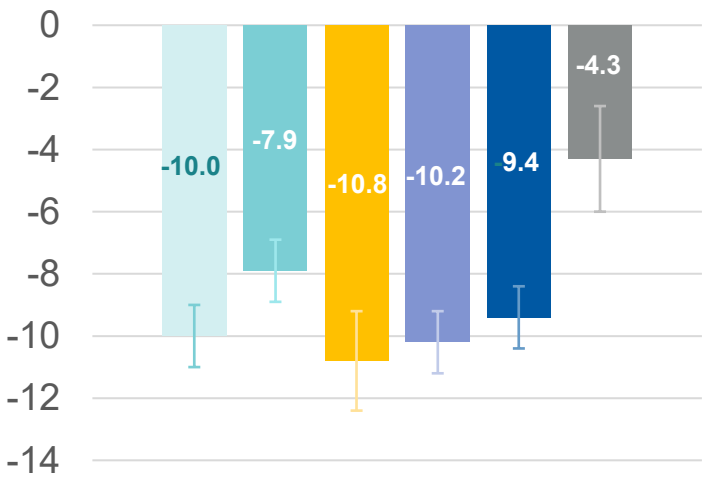
[a] Pool of multiple PTs: Injection site bruising, Injection site discoloration, Injection site erythema, Injection site irritation, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction
[b] Pool of multiple PTs: Abdominal pain, Abdominal pain upper, Abdominal pain lower
AE = Adverse event. d = dose. n = number of participants in the full analysis set. n = number of participants with at least one AE. % = percent of participants reporting at least one AE.
Data on file.

Estimated changes in selected cardiovascular risk factors

Secondary endpoints (W42): Efficacy estimand*

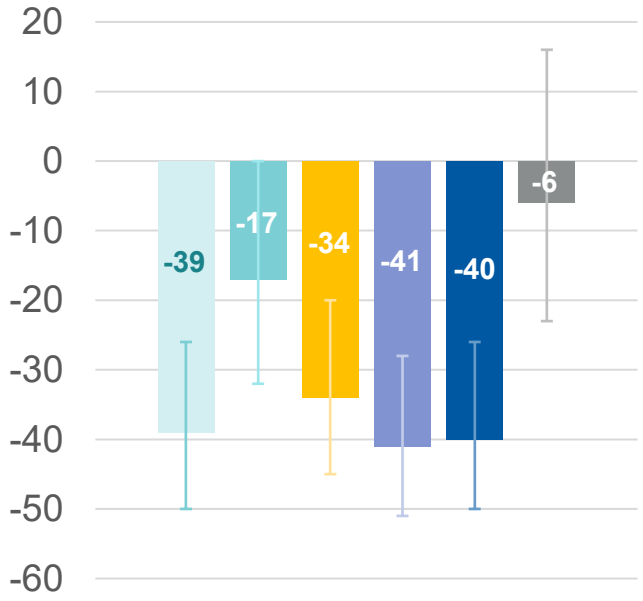
Waist circumference (cm)

Baseline 114 cm



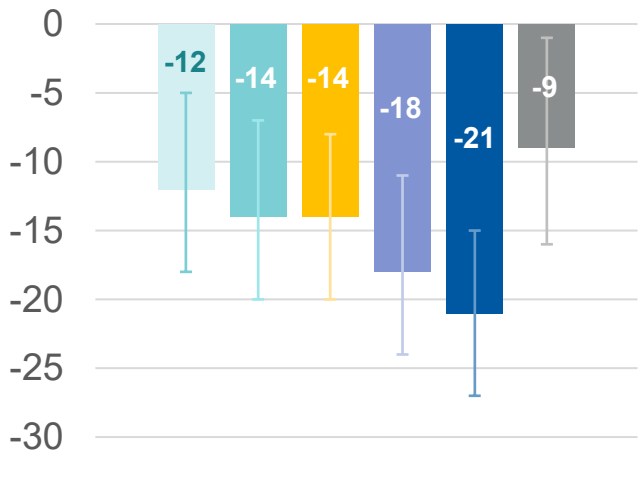
hsCRP (%)

Baseline 4.2 mg/L



Triglycerides (%)

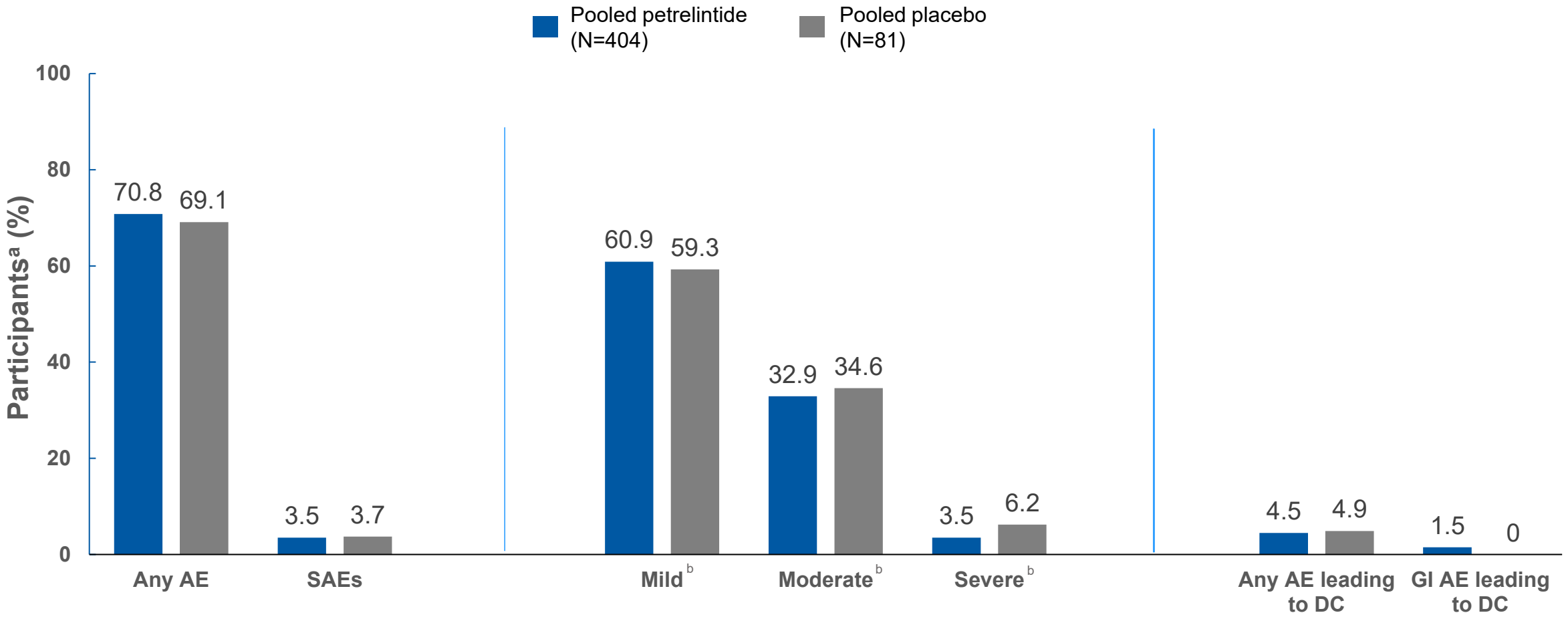
Baseline 1.57 mmol/L



Dose 1 Dose 2 Dose 3 Dose 4 Dose 5 Pooled Placebo

*Treatment effect if all participants had remained on investigational medicinal product (IMP) and not initiated other anti-obesity treatment. Error bars represent confidence interval.
hsCRP, high-sensitivity C-reactive protein.
Data on file.

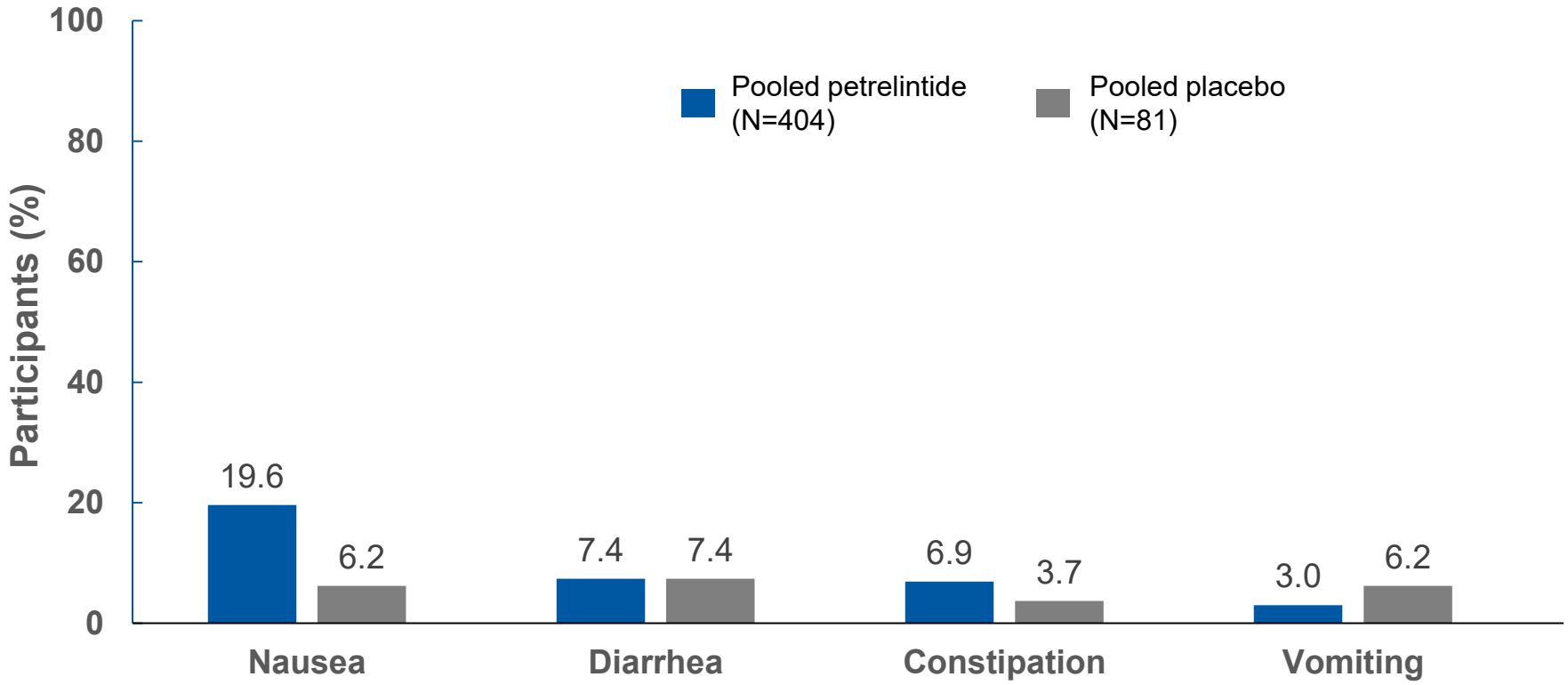
AE overview – pooled petrelintide vs pooled placebo



[a] Participants reporting at least one AE; [b] Mild: no or transient symptoms, no interference with the participant's daily activities. Moderate: marked symptoms, moderate interference with the participant's daily activities. Severe: a type of AE that interrupts usual activities of daily living or significantly affects clinical status or may require intensive therapeutic intervention. A severe reaction does not necessarily deem the AE as serious, and an SAE is not always severe in nature.
AE, adverse event; DC, discontinuation; GI, gastrointestinal; SAE, serious adverse event. Safety data collected until week 51 (end of trial)
Data on file.

AE overview - selected GI AEs

Most GI AEs with petrelintide were mild (77%) and reported during dose escalation



AE, adverse events; GI, gastrointestinal. Safety data collected until week 51 (end of trial)
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Summary

- In this Phase 2 dose finding trial, petrelintide demonstrated statistically significant and clinically meaningful weight reduction across all dose cohorts at both Week 28 and through Week 42 in a gender-balanced population
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