Received: 27 January 2025 | Revised: 29 April 2025 | Accepted: 1 May 2025

DOI: 10.1002/oby.24329

ORIGINAL ARTICLE

Clinical Trials and Investigations

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Long-acting PYY_{3-36} analogue with semaglutide for obesity: from preclinical assessment through randomized clinical studies

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Funding information
Novo Nordisk A/S

Abstract

Objective: The hormone peptide YY (PYY; cleaved into Y_2-selective form PYY_{3-36}) is an attractive candidate for use as a complementary pharmacotherapy for obesity along with glucagon-like peptide-1 (GLP-1) receptor agonists. This series of studies investigated a novel long-acting PYY_{3-36} analogue (PYY1875) alone and as an add-on to semaglutide for treatment of obesity.

Methods: Weight loss and food intake were first investigated in obese male rats, followed by phase 1 and 2 clinical studies investigating efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of PYY1875 as monotherapy and in combination with semaglutide in participants with overweight or obesity.

Results: PYY1875 induced additional body weight loss in semaglutide-treated obese rats. In the phase 1 study, all doses of PYY1875 alone and coadministered with semaglutide were tolerated. In the phase 2 study, a modest but not clinically meaningful treatment effect of PYY1875 1.0 mg versus placebo as an add-on to semaglutide 2.4 mg was observed. However, gastrointestinal-related adverse events were common with the 1.0-mg PYY1875 dose, and the 2.0-mg PYY1875 dose escalation regimen was not tolerated (both as add-ons to semaglutide).

Conclusions: PYY1875 showed modest efficacy as an add-on to semaglutide for weight management in people with obesity, but the treatment was not well tolerated.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as once-daily liraglutide and once-weekly semaglutide, play significant roles in the treatment of obesity and type 2 diabetes as an adjunct to diet and exercise [1, 2]. The hormone peptide YY (PYY) is co-secreted with GLP-1 by L-cells in the distal gut in response to nutrient intake [3]. PYY is secreted as a 36-amino acid peptide, PYY_{1-36}, which is cleaved into inactive PYY_{3-34} and active PYY_{3-36}, the latter of which plays a role in the regulation of hunger and satiety in the central nervous

system alongside GLP-1 [4–6]. In contrast to GLP-1, which binds a single receptor, PYY can bind and activate four neuropeptide Y receptors: Y_1 and Y_5, which stimulate food intake when activated, as well as Y_2 and to a lesser extent Y_4, which inhibit food intake [7–10]. PYY_{3-36} binds with high affinity to the Y_2 receptor and has been shown to reduce food intake, lower body weight, and improve insulin sensitivity in several animal species [6, 11–14]. PYY_{3-36} also reduces acute food intake in humans [6, 15, 16]. There is considerable interest in investigating potential additive or synergistic effects of administering PYY and GLP-1 analogues in combination [17, 18]. Indeed, co-infusion of PYY_{3-36} and GLP-1 analogues appears to exert a synergistic suppressive effect on energy intake in humans and nonhuman species [15, 17, 19, 20].

Prolonged exposure to PYY_{3-36} is necessary to obtain maximum therapeutic effect. However, PYY_{3-36} has a short half-life ($t_{1/2}$) of roughly 10 min [5, 21], and supraphysiological doses of PYY_{3-36} cause nausea, which limits dosing [22, 23]. This narrow therapeutic window might be mitigated by increasing the $t_{1/2}$ and by up-titration. NNC0165-1875 (PYY1875, for short) is a novel long-acting PYY_{3-36} analogue and a selective Y_2 receptor agonist [24], intended for chronic weight management by subcutaneous (s.c.) administration in combination with semaglutide. The chemical structure of PYY1875 and its specificity to the Y_2 receptor have been described previously [24]. The studies described here were conducted as part of the preclinical and early clinical development program for PYY1875. The clinical studies examined the efficacy, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) parameters of PYY1875 as monotherapy and in combination with semaglutide in people with overweight or obesity.

Study Importance

What is already known?

- The hormone peptide YY (PYY), particularly its Y_2 receptor-selective form PYY_{3-36}, is known to play a role in regulating hunger and satiety and has shown potential in reducing food intake and body weight in both animals and humans.
- There is significant interest in the combined use of PYY_{3-36} analogues and glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, due to their synergistic effects on suppressing energy intake.

What does this study add?

- The long-acting PYY_{3-36} analogue PYY1875 showed modest efficacy as an add-on to semaglutide for weight management in people with obesity but not at a clinically meaningful level.
- PYY1875 treatment as an add-on to semaglutide was not well tolerated using the dosing regimen applied here.

How might these results change the direction of research or focus of clinical practice?

- Further research is needed to develop more tolerable PYY_{3-36} formulations and to optimize dosing regimens in order to minimize adverse effects.

METHODS

Preclinical studies in diet-induced obese rats

Weight loss and food intake were investigated in male Sprague Dawley rats. In the first experiment, the animals were dosed once daily with 3, 30, or 100 nmol/kg of semaglutide or vehicle, s.c., for 4 weeks ($n = 9$ each). Semaglutide up-titration steps were 1, 3, 10, 30, and 100 nmol/kg on study days 0 to 4, respectively. Food intake and body weight were monitored daily at 9 a.m.

The second experiment studied four groups of nine rats each that were treated daily with combinations of semaglutide or semaglutide-vehicle and PYY1875 or PYY1875-vehicle, s.c. The first group was dosed with PYY1875-vehicle and semaglutide-vehicle, the second group with 30 nmol/kg of PYY1875 and semaglutide-vehicle, the third group with PYY1875-vehicle and 30 nmol/kg of semaglutide, and the fourth group with 3 nmol/kg of PYY1875 on days 1 to 16 and 30 nmol/kg of PYY1875 on days 17 to 26 in combination with 30 nmol/kg of semaglutide. Both semaglutide and PYY1875 were uptitrated daily at 10%, 20%, 40%, 60%, 80%, and finally 100% of full dose on study day 6. Body weight and food intake were recorded daily. Blood samples to measure plasma exposure levels of semaglutide and PYY1875 were collected 1 h after the final dose. Data were analyzed via one-way ANOVA followed by Bonferroni's multiple comparisons test using GraphPad Prism version 9.0.1 (GraphPad Software).

Phase 1 clinical study

First-in-human study design and population

This first-in-human phase 1 study was an interventional, single-center, randomized, double-blind (within cohorts), placebo-controlled, single-dose, ascending-dose clinical study (ClinicalTrials.gov identifiers NCT03707990 and NCT04969939). The study was conducted at Celerion (Tempe, Arizona) between October 15, 2018, and August 13, 2019, and recruited adult male participants (18–55 years; ≥70 kg; body mass index [BMI] = 25.0–34.9 kg/m^2; glycated hemoglobin [HbA1c] < 6.5%). Exclusion criteria can be found in Online Supporting Information Methods.

The study consisted of two parts. In part 1, participants were assigned in screening order to one of five cohorts to receive a single

dose of 0.1, 0.3, 0.6, 1.2, or 2.1 mg of PYY1875 or placebo (randomized 6:2, PYY1875:placebo), starting with the lowest dose cohort. In part 2, all participants received 0.25-mg semaglutide and were assigned in screening order to one of six cohorts to receive a single dose of 0.03-, 0.1-, 0.3-, 0.6-, 1.2-, or 1.7-mg PYY1875 or placebo (randomized 6:2, PYY1875:placebo), starting with the lowest dose cohort. In both parts, randomization was completed according to a list provided by the sponsor. All treatments were administered by use of syringes and needles by qualified site staff. Sentinel dosing was applied, that is, the first two participants in each dose cohort were dosed (randomized 1:1, PYY1875:placebo) before the remaining participants (randomized 5:1, PYY1875:placebo), starting from the lowest dose. Participants stayed at the facility for a 5-day safety observation period. PYY1875 was blinded to matching placebo, whereas semaglutide was open-label.

Safety endpoints and assessments

The primary objective was to investigate the safety and tolerability of a single s.c. dose of PYY1875 as monotherapy and in combination with a single s.c. dose of 0.25-mg semaglutide in participants with overweight or obesity. The primary endpoint was the number of treatment emergent adverse events (TEAEs) from day 1 to follow-up at day 36. As the $t_{1/2}$ of PYY1875 determined in the 0.1- and 0.3-mg cohorts of part 1 was longer than expected from preclinical data, an additional visit at day 54 was added for the rest of the cohorts except for the 0.03-mg cohort in part 2. A potential relationship of TEAEs with the study drug was assessed by the investigator. Exploratory safety endpoints included number of injection site reactions, occurrence of antidrug antibodies, and change from baseline to follow-up in clinical laboratory tests, vital signs, physical examination, and electrocardiography.

PK and PD endpoints

Secondary and exploratory PK endpoints were included for PYY1875 in part 1 and part 2 and for semaglutide part 2. Included endpoints were areas under the concentration-time curve $AUC_{0\text{-}INF}$ and $AUC_{0\text{-}168h}$, maximum plasma concentration (C_{max}), t_{max}, and $t_{1/2}$ after a single s.c. dose. Exploratory PD endpoints for part 1 and 2 were change in body weight as well as glucose, glucagon, insulin, C-peptide, ghrelin, leptin, and soluble leptin receptor, all fasted and from day −1 to day 4.

Clinical laboratory and statistical analyses are detailed in Online Supporting Information Methods.

Phase 2 clinical study

Dose-finding study design and population

The phase 2 study recruited male and female adult participants with obesity (BMI = 30.0–45.0; HbA1c < 6.5%; exclusion criteria in Online Supporting Information Methods) across 14 sites in the United States between July 15, 2021, and January 31, 2023, and consisted of two parts. Part 1 was a 16-week, four-armed, double-blinded, randomized, placebo-controlled, single-site study comparing coescalation of two once-weekly doses of PYY1875, 1.0 and 2.0 mg, versus placebo as an add-on to open-label semaglutide s.c. 2.4 mg. Participants were randomized 2:1:2:1 to the two doses of PYY1875 or placebo (i.e., 2:1 at each dose level) along with semaglutide, based on a randomization list. The follow-up period was 8 weeks.

Part 2 was a 48-week, four-armed, double-blinded (within dose level), randomized, placebo-controlled, multicenter (13 sites in the US), proof-of-principle study comparing once-weekly PYY1875 versus placebo as an add-on to open-label, once-weekly semaglutide (s.c. 2.4 mg). Part 2 consisted of part 2a and part 2b. Part 2a was an open-label run-in in which all participants were treated with once-weekly semaglutide (s.c. 2.4 mg at steady state) for 32 weeks, including an 8-week escalation period.

Part 2b was the main study period, which took place during weeks 32 to 48, with week 32 considered baseline and week 48 end of treatment (EOT). In this period, all participants were randomized 2:1 to one of two once-weekly PYY1875 doses (1.0/2.0 mg) or placebo as an add-on to the ongoing semaglutide (s.c. 2.4 mg). The first 12 participants (across three sites) were allocated to the 2.0-mg dose (2:1, PYY1875:placebo), and the rest were allocated to the 1.0-mg dose (also 2:1, PYY1875:placebo). Participants were randomized using an interactive web response system and assigned to the next available treatment according to the randomization schedule. The 1.0-mg PYY1875 dose was assessed for efficacy and safety whereas the 2.0-mg dose was only assessed for safety. PYY1875 or placebo was escalated at 2-week intervals over 8 or 10 weeks to 1.0-mg or 2.0-mg PYY1875, respectively. This was followed by 8 (1.0 mg) or 6 (2.0 mg) weeks of maintenance dose. Total study duration of part 2 was 58 weeks: 2 weeks of screening, 32 weeks of semaglutide run-in, 16 weeks of PYY1875 or placebo as an add-on to semaglutide, and 8 weeks of follow-up with end of study (EOS) at week 56.

PYY1875 s.c. doses were provided in a 0.2/5.0-mg/mL-strength NovoPen 4 (Novo Nordisk), placebo in a 0-mg/mL-strength NovoPen 4, and semaglutide in a 3.0-mg/mL-strength PDS290 prefilled pen-injector (Novo Nordisk). On-site dosing was administered by the investigator or delegated staff whereas dosing at home was self-administered.

Exclusion criteria included HbA1c ≥6.5% and a history of type 1 or type 2 diabetes (full list of exclusion criteria in Online Supporting Information Methods).

Safety endpoints and assessments

The primary endpoint in part 1 was the number of TEAEs from dosing (day 1) to EOS (week 24). The numbers of TEAEs and serious TEAEs from week 0 to EOS (week 56) were supportive secondary safety endpoints in part 2 (1.0- and 2.0-mg PYY1875).

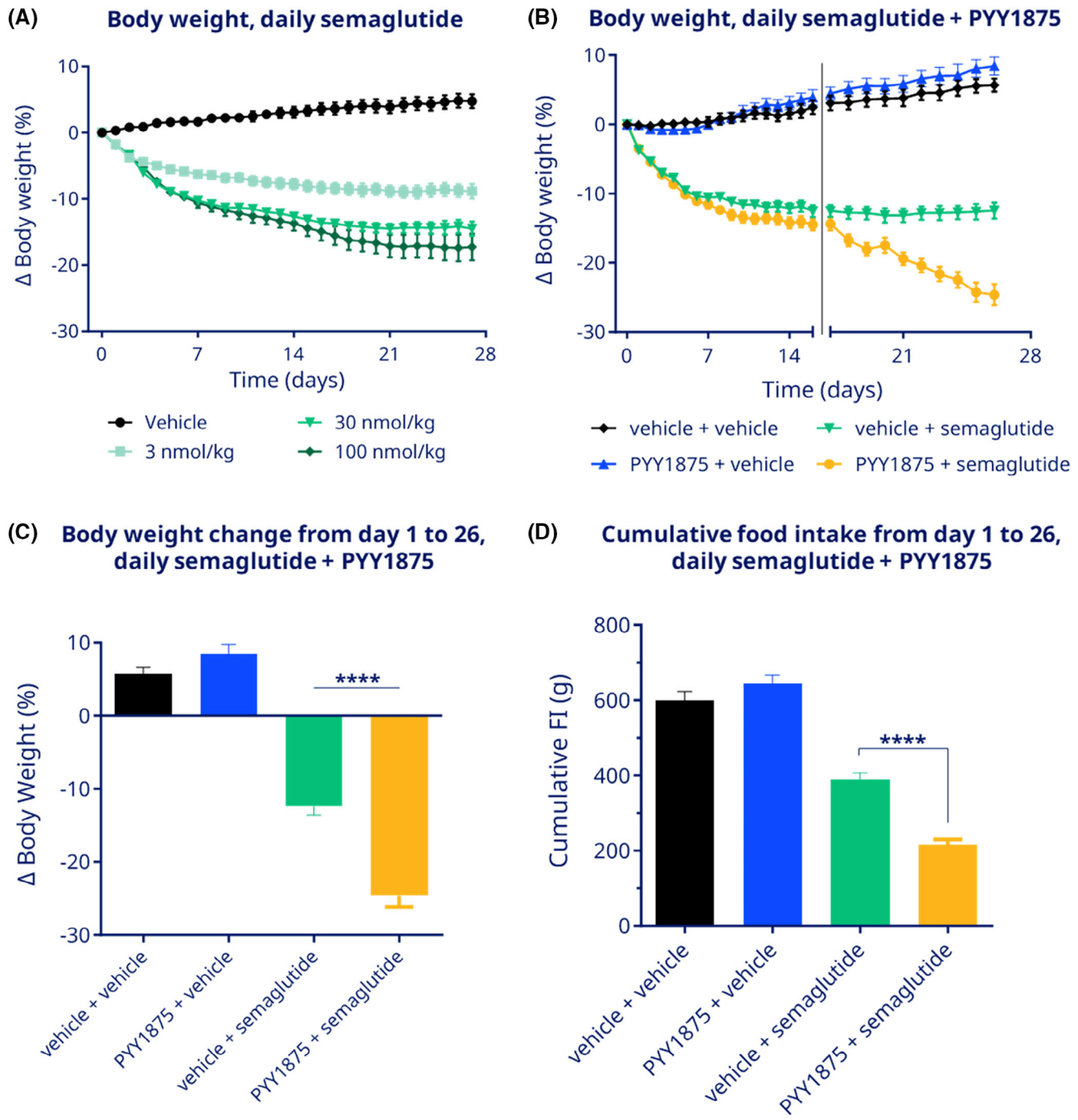

FIGURE 1 Preclinical studies in diet-induced obese rats. (A) Change in body weight during daily s.c. doses of semaglutide (3, 30, or 100 nmol/kg) or vehicle. (B) Change in body weight over 26 days of daily s.c. treatment with semaglutide-vehicle + PYY1875-vehicle ("vehicle + vehicle"), 30 nmol/kg of PYY1875 + semaglutide-vehicle ("PYY1875 + vehicle"), PYY1875-vehicle + 30 nmol/kg of semaglutide ("vehicle + semaglutide"), or 3/30 nmol/kg of PYY1875 + 30 nmol/kg of semaglutide ("PYY1875 + semaglutide"). In the last group, rats received 3 nmol/kg of PYY1875 on days 1–16 and 30 nmol/kg of PYY1875 on days 17–26 while semaglutide was dosed at 30 nmol/kg throughout. (C) Weight loss and (D) cumulative food intake after 26 days of daily s.c. treatment with the combinations of semaglutide + PYY1875 described in panel B. Mean ± SEM values are graphed. One-way ANOVA with Bonferroni's multiple comparisons test was used for statistical testing in panels C and D. ****$p < 0.0001$. FI, food intake; s.c., subcutaneous. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Phase 1 study, part 1: TEAEs in the SAS.

	PYY1875 0.1 mg	PYY1875 0.3 mg	PYY1875 0.6 mg	PYY1875 1.2 mg	PYY1875 2.1 mg	Placebo	Total
Number of participants	6	6	6	6	6	10	40
Events	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	3 (50.0) 10	4 (66.7) 26	6 (60.0) 30	21 (52.5) 89
Serious							
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
No	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	3 (50.0) 10	4 (66.7) 26	6 (60.0) 30	21 (52.5) 89
Events leading to withdrawal	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Severity							
Severe	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 2	0 (0.0) 0	1 (2.5) 2
Moderate	0 (0.0) 0	1 (16.7) 2	1 (16.7) 7	1 (16.7) 2	1 (16.7) 4	3 (30.0) 3	7 (17.5) 18
Mild	2 (33.3) 4	3 (50.0) 6	2 (33.3) 4	3 (50.0) 8	4 (66.7) 20	6 (60.0) 27	20 (50.0) 69
Related to study product							
Probable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	4 (66.7) 15	0 (0.0) 0	4 (10.0) 15
Possible	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (33.3) 8	2 (33.3) 4	2 (20.0) 3	6 (15.0) 15
Unlikely	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	1 (16.7) 2	3 (50.0) 7	5 (50.0) 27	17 (42.5) 59
Related to technical complaint							
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
No	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	3 (50.0) 10	4 (66.7) 26	6 (60.0) 30	21 (52.5) 89
Injection site reaction							
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	0 (0.0) 0	1 (2.5) 1
No	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	3 (50.0) 10	4 (66.7) 25	6 (60.0) 30	21 (52.5) 88
Outcome							
Fatal	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not recovered/not resolved	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (10.0) 1	1 (2.5) 1
Recovered/resolved with sequelae	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Recovering/resolving	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Recovered/resolved	2 (33.3) 4	3 (50.0) 8	3 (50.0) 11	3 (50.0) 10	4 (66.7) 26	5 (50.0) 29	20 (50.0) 88
Unknown	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Most common AEs by SOC (≥10% of participants)							
Nervous system disorders	2 (33.3) 2	0 (0.0) 0	2 (33.3) 2	2 (33.3) 3	3 (50.0) 6	2 (20.0) 2	11 (27.5) 15
Gastrointestinal disorders	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 4	3 (50.0) 8	5 (50.0) 9	9 (22.5) 21
General disorders and administration site conditions	0 (0.0) 0	1 (16.7) 3	1 (16.7) 1	2 (33.3) 3	2 (33.3) 2	3 (30.0) 9	9 (22.5) 18

(Continues)

TABLE 1 (Continued)

	PYY1875 0.1 mg	PYY1875 0.3 mg	PYY1875 0.6 mg	PYY1875 1.2 mg	PYY1875 2.1 mg	Placebo	Total
Respiratory, thoracic, and mediastinal disorders	0 (0.0) 0	1 (16.7) 2	0 (0.0) 0	0 (0.0) 0	1 (16.7) 3	2 (20.0) 3	4 (10.0) 5
Skin and s.c. tissue disorders	1 (16.7) 1	0 (0.0) 0	1 (16.7) 1	0 (0.0) 0	0 (0.0) 0	2 (20.0) 3	4 (10.0) 5

Note: Data are expressed as *n* (%) *E*, where *n* is the number of participants reporting an event, % is the percentage of participants reporting an event, and *E* is the number of events.
Abbreviations: AE, adverse event; s.c., subcutaneous; SAS, safety analysis set; SOC, system organ class; TEAE, treatment emergent adverse event.

PD endpoints and PK assessments

PD endpoints were only assessed in part 2 of the phase 2 study and only for participants receiving the 1.0-mg PYY1875 dose. The primary PD endpoint was change (percentage) in body weight from baseline (i.e., randomization at week 32) to EOT (week 48), whereas supportive secondary endpoints were change from baseline to EOT in body weight (kilograms), HbA1c (percentage points), fasting plasma glucose (millimoles/liter), fasting insulin (picomoles/liter), and waist circumference (centimeters), as well as relative change (ratio to baseline) in total, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) cholesterol, triglycerides, and free fatty acids. Results reflect the treatment effect of 1.0-mg PYY1875 in the full analysis set regardless of treatment status at EOT. Furthermore, plasma concentrations of PYY1875 and semaglutide for PK analyses were determined throughout part 1 and in part 2b.

Clinical laboratory and statistical analyses are detailed in Online Supporting Information Methods.

Ethics

Preclinical studies were conducted under approvals 2013-15-1934-00875 and 2014-15-0201-00142 from the Danish Animal Experiments Inspectorate. The clinical studies were conducted in accordance with the Declaration of Helsinki [25], the Council for International Organizations of Medical Sciences International Ethical Guidelines [26], and the International Conference on Harmonization Good Clinical Practice Guideline [27]. The clinical study protocols were reviewed by the independent ethics committees/institutional review boards of Advarra Inc. for the phase 1 study and with WCG as the central institutional review board for the phase 2 study, but one site used Baylor Scott & White Research Institute. All participants provided written informed consent before participating in the studies.

RESULTS

Preclinical studies in DIO rats

Diet-induced obese (DIO) rats that were treated with 3-, 30-, or 100-nmol/kg daily doses of s.c. semaglutide showed a mean (SD) of −8.8% (2.9%), −14.2% (3.0%), or −17.4% (5.7%) body weight loss, respectively, after 26 days of treatment, whereas vehicle-treated rats gained 4.8% (2.8%) body weight (Figure 1A). After 26 days of combined treatment with semaglutide and PYY1875 (Figure 1B,C), mean body weight increased by 5.7% (2.8%) in the vehicle + vehicle group and by 8.4% (4.0%) in the 30 nmol/kg PYY1875 + vehicle group, while decreasing by −12.5% (3.4%) in the vehicle + 30 nmol/kg semaglutide group and −24.6% (4.6%) in the 3/30 nmol/kg PYY1875 + 30

TABLE 2 Phase 1 study, part 2: TEAEs in the SAS.

	PYY1875 0.03 mg, semaglutide 0.25 mg	PYY1875 0.1 mg, semaglutide 0.25 mg	PYY1875 0.3 mg, semaglutide 0.25 mg	PYY1875 0.6 mg, semaglutide 0.25 mg	PYY1875 1.2 mg, semaglutide 0.25 mg	PYY1875 1.7 mg, semaglutide 0.25 mg	Placebo, semaglutide 0.25 mg	Total
Number of participants	6	6	6	6	6	6	12	48
Events	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 20	6 (100.0) 30	6 (50.0) 9	34 (70.8) 116
Serious								
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
No	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 20	6 (100.0) 30	6 (50.0) 9	34 (70.8) 116
Events leading to withdrawal	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Severity								
Severe	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Moderate	1 (16.7) 1	0 (0.0) 0	0 (0.0) 0	1 (16.7) 6	4 (66.7) 8	3 (50.0) 5	1 (8.3) 1	10 (20.8) 21
Mild	4 (66.7) 8	3 (50.0) 19	5 (83.3) 16	4 (66.7) 7	4 (66.7) 12	6 (100.0) 25	6 (50.0) 8	32 (66.7) 95
Related to PYY1875								
Probable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	4 (66.7) 11	3 (50.0) 9	0 (0.0) 0	7 (14.6) 20
Possible	0 (0.0) 0	0 (0.0) 0	2 (33.3) 6	0 (0.0) 0	3 (50.0) 5	3 (50.0) 4	1 (8.3) 1	9 (18.8) 16
Unlikely	4 (66.7) 9	3 (50.0) 19	5 (83.3) 10	4 (66.7) 13	2 (33.3) 4	5 (83.3) 17	5 (41.7) 8	28 (58.3) 80
Related to semaglutide								
Probable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	4 (66.7) 11	3 (50.0) 9	0 (0.0) 0	7 (14.6) 20
Possible	0 (0.0) 0	0 (0.0) 0	2 (33.3) 4	0 (0.0) 0	3 (50.0) 5	4 (66.7) 6	1 (8.3) 1	10 (20.8) 16
Unlikely	4 (66.7) 9	3 (50.0) 19	5 (83.3) 12	4 (66.7) 13	2 (33.3) 4	4 (66.7) 15	5 (41.7) 8	27 (56.3) 80
Related to technical complaint/PYY1875								
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
No	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 20	6 (100.0) 30	6 (50) 9	34 (70.8) 116
Related to technical complaint/ semaglutide								
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
No	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 20	6 (100.0) 30	6 (50) 9	34 (70.8) 116
Injection site reaction/PYY1875								
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	0 (0.0) 0	0 (0.0) 0	1 (2.1) 1
No	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 19	6 (100.0) 30	6 (50) 9	34 (70.8) 115
Injection site reaction/semaglutide								
Yes	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	2 (33.3) 2	0 (0.0) 0	3 (6.3) 3
No	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 19	6 (100.0) 28	6 (50) 9	34 (70.8) 113

(Continues)

TABLE 2 (Continued)

	PYY1875 0.03 mg, semaglutide 0.25 mg	PYY1875 0.1 mg, semaglutide 0.25 mg	PYY1875 0.3 mg, semaglutide 0.25 mg	PYY1875 0.6 mg, semaglutide 0.25 mg	PYY1875 1.2 mg, semaglutide 0.25 mg	PYY1875 1.7 mg, semaglutide 0.25 mg	Placebo, semaglutide 0.25 mg	Total
Outcome								
Fatal	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not recovered/not resolved	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Recovered/resolved with sequelae	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Recovering/resolving	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Recovered/resolved	4 (66.7) 9	3 (50.0) 19	5 (83.3) 16	4 (66.7) 13	6 (100.0) 19	6 (100.0) 30	6 (50.0) 9	34 (70.8) 115
Unknown	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	0 (0.0) 0	0 (0.0) 0	1 (2.1) 1
Most common AEs by SOC (≥10% of participants)								
Gastrointestinal disorders	1 (16.7) 1	1 (16.7) 2	2 (33.3) 3	2 (33.3) 2	5 (83.3) 11	5 (83.3) 8	1 (8.3) 1	17 (35.4) 28
Nervous system disorders	3 (50.0) 4	2 (33.3) 4	1 (16.7) 1	2 (33.3) 2	2 (33.3) 2	2 (33.3) 3	1 (8.3) 1	13 (27.1) 17
General disorders and administration site conditions	0 (0.0) 0	1 (16.7) 2	1 (16.7) 1	1 (16.7) 1	1 (16.7) 2	4 (66.7) 6	1 (8.3) 1	9 (18.8) 13
Respiratory, thoracic, and mediastinal disorders	1 (16.7) 1	3 (50.0) 6	2 (33.3) 3	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	1 (8.3) 2	8 (16.7) 13
Musculoskeletal and connective tissue disorders	1 (16.7) 1	1 (16.7) 2	2 (33.3) 2	1 (16.7) 2	0 (0.0) 0	2 (33.3) 3	1 (8.3) 1	8 (16.7) 10
Investigations	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	1 (16.7) 3	2 (33.3) 3	0 (0.0) 0	1 (8.3) 1	7 (14.6) 10
Metabolism and nutrition disorders	0 (0.0) 0	0 (0.0) 0	1 (16.7) 1	0 (0.0) 0	2 (33.3) 2	3 (50.0) 4	1 (8.3) 1	7 (14.6) 8

Note: Data are expressed as *n* (%) *E*, where *n* is the number of participants reporting an event, % is the percentage of participants reporting an event, and *E* is the number of events.
Abbreviations: AE, adverse event; SAS, safety analysis set; SOC, system organ class; TEAE, treatment emergent adverse event.

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nmol/kg semaglutide group. Semaglutide and PYY1875 plasma exposures were independent of each other (Figure S1). In the same experiment, mean (SD) cumulative food intake from day 1 to 26 was 600 (70) g in the vehicle + vehicle group, 645 (67) g in the 30 nmol/kg PYY1875 + vehicle group, 389 (53) g in the vehicle + 30 nmol/kg semaglutide group, and 215 (44) g in the 3/30 nmol/kg PYY1875 + 30 nmol/kg semaglutide group. These promising efficacy results supported advancing PYY1875 into clinical studies as a potential add-on for weight management in semaglutide-treated individuals with obesity and overweight.

Phase 1 clinical study

Disposition, baseline characteristics, and dose levels

A total of 88 male participants were included in the first-in-human study. The participants were divided into part 1 to receive PYY1875 (40 participants aged 21–50 years; BMI = 25.4–35.0 kg/m^2) and part 2 to receive PYY1875 in combination with semaglutide (48 participants aged 22–50 years;

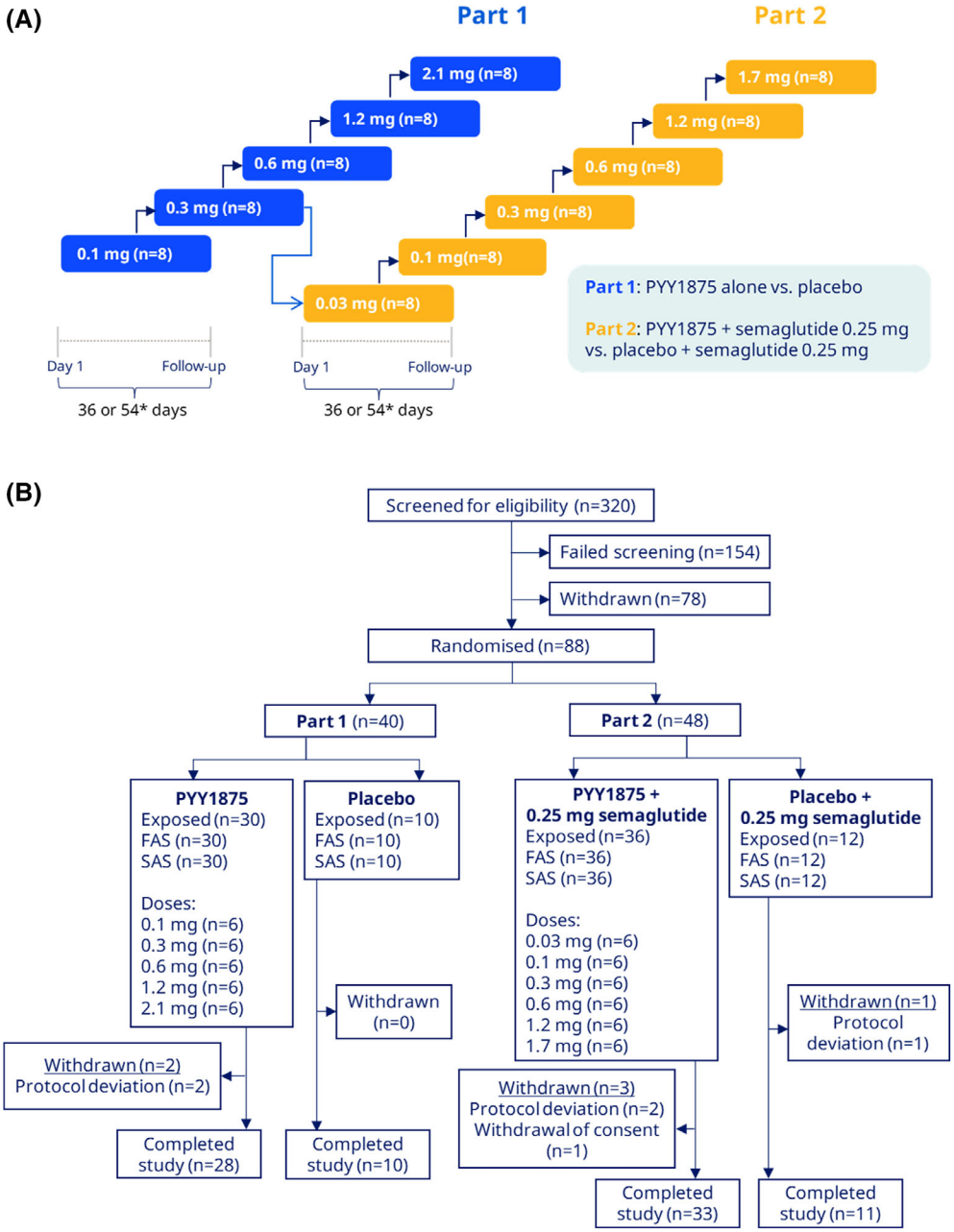
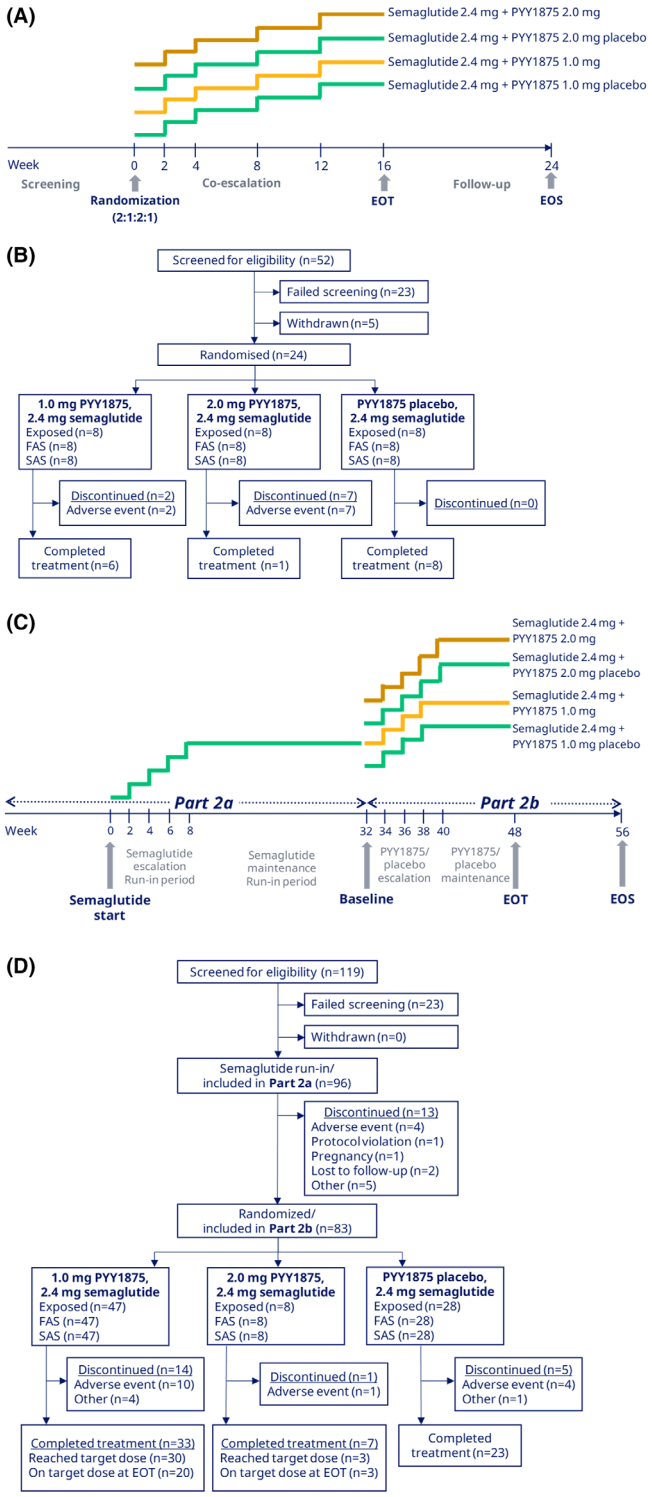


FIGURE 2 Phase 1 study design and participant disposition. (A) PYY1875 alone (part 1) and upon coadministration with a single dose of semaglutide (part 2) in participants with overweight and obesity. In all cohorts, participants were randomized 6:2 to active treatment or placebo. The arrow indicates that enrollment in the 0.03-mg cohort in part 2 began after completion of the 0.3-mg cohort in part 1. (B) Participant disposition. *Visit at 54 days was not included in the 0.1- or 0.3-mg cohort in part 1 or in the 0.03-mg cohort in part 2. FAS, full analysis set; SAS, safety analysis set. [Color figure can be viewed at wileyonlinelibrary.com]

BMI = 25.8–35.5 kg/m^2; Figure 2A). Baseline characteristics are available in Table S1 (part 1) and S2 (part 2). In part 1, two participants were withdrawn due to protocol deviations (Figure 2B). In part 2, three participants were withdrawn due to protocol deviations, and one participant withdrew consent (Figure 2B). A total of 38 (95%) participants in part 1 and 44 (91.7%) participants in part 2 completed the study.



Safety and tolerability

Summary statistics for TEAEs are shown in Table 1 (part 1) and in Table 2 (part 2). All doses of PYY1875 alone and coadministered with semaglutide were tolerated. Higher doses may require dose escalation to limit gastrointestinal adverse events (AEs; nausea and vomiting). Two participants had mild injection site reactions in the higher PYY1875 dose treatment groups (tenderness and itching). No anti-PYY1875 antibodies were detected in PYY1875 treatment groups. No dose–response effect was observed for other safety parameters (vital signs, electrocardiogram, mental health assessment, 24-h urine). There were no fatal events.

PK and PD

PK properties of PYY1875 and semaglutide were independent of each other. The increase of PYY1875 exposure with increasing dose levels was consistent with dose-proportionality (Figure S2A). The PYY1875 $t_{1/2}$ was around 10 days (Tables S3 and S4), supporting once-weekly dosing. During the 5-day in-house period, a transient decrease in body weight (0.4–2.3 kg) was observed with no dose–response effect when PYY1875 was coadministered with semaglutide (Figure S2B). No clinically relevant changes were observed for fasting glucose or gastrointestinal parameters in either part of the study. Together, the single-dose phase 1 results supported potential efficacy and tolerability of PYY1875 in combination with semaglutide for weight management and justified progression to the phase 2 study.

Phase 2 clinical study

Disposition, baseline characteristics, and dose levels

A total of 24 participants with obesity were randomized within part 1 (Figure 3A,B), in which the participants received either once-weekly 1.0-mg or once-weekly 2.0-mg PYY1875 or placebo coescalated with

FIGURE 3 Phase 2 study design. (A) Design of part 1 investigating safety and tolerability of coescalation of two dose levels of PYY1875 (1.0 and 2.0 mg) and semaglutide administered simultaneously as separate doses in participants with obesity. (B) Participant disposition in part 1. (C) Design of part 2a (semaglutide s.c. 2.4 mg run-in) and part 2b (continued semaglutide s.c. 2.4 mg plus PYY1875 1.0 mg, PYY1875 2.0 mg, or PYY1875 placebo). (D) Participant disposition in part 2. Dose escalation steps for semaglutide are 0.25, 0.5, 1.0, 1.7, and 2.4 mg at intervals indicated in panels A and C. Dose escalation steps for 1.0-mg PYY1875 are 0.05, 0.1, 0.25, 0.5, and 1.0 mg at intervals indicated in panels A and C. Dose escalation steps for 2.0-mg PYY1875 are 0.1, 0.25, 0.5, 1.0, and 2.0 mg in part 1 and 0.05, 0.1, 0.25, 0.5, 1.0, and 2.0 mg in part 2 at intervals indicated in panels A and C. EOS, end of study; EOT, end of treatment; FAS, full analysis set; SAS, safety analysis set; s.c., subcutaneous. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Phase 2 study, part 1: TEAEs in the SAS.

	PYY1875 1.0 mg, semaglutide 2.4 mg	PYY1875 2.0 mg, semaglutide 2.4 mg	Placebo, semaglutide 2.4 mg	Total
Number of participants	8	8	8	24
Events	8 (100.0) 56	8 (100.0) 71	8 (100.0) 37	24 (100.0) 164
Serious				
Yes	0	1 (12.5) 1	0	1 (4.2) 1
No	8 (100.0) 56	8 (100.0) 70	8 (100.0) 37	24 (100.0) 163
Events leading to withdrawal	2 (25.0) 5	7 (87.5) 12	0	9 (37.5) 17
Severity				
Severe	0	1 (12.5) 1	1 (12.5) 1	2 (8.3) 2
Moderate	4 (50.0) 11	5 (62.5) 16	2 (25.0) 5	11 (45.8) 32
Mild	8 (100.0) 45	8 (100.0) 54	8 (100.0) 31	24 (100.0) 130
Related to PYY1875				
Probable	7 (87.5) 38	8 (100.0) 50	7 (87.5) 15	22 (91.7) 103
Possible	4 (50.0) 7	3 (37.5) 8	6 (75.0) 12	13 (54.2) 27
Unlikely	6 (75.0) 11	6 (75.0) 13	4 (50.0) 10	16 (66.7) 34
Related to semaglutide				
Probable	7 (87.5) 38	8 (100.0) 50	7 (87.5) 14	22 (91.7) 102
Possible	4 (50.0) 8	3 (37.5) 8	5 (62.5) 10	12 (50.0) 26
Unlikely	6 (75.0) 10	6 (75.0) 13	6 (75.0) 13	18 (75.0) 36
Action taken to PYY1875				
Drug withdrawn	2 (25.0) 5	7 (87.5) 12	0	9 (37.5) 17
Drug interrupted	1 (12.5) 1	1 (12.5) 1	1 (12.5) 4	3 (12.5) 6
Dose not changed	8 (100.0) 41	8 (100.0) 50	8 (100.0) 32	24 (100.0) 123
Not applicable	3 (37.5) 9	5 (62.5) 8	1 (12.5) 1	9 (37.5) 18
Action taken to semaglutide				
Drug withdrawn	2 (25.0) 5	7 (87.5) 12	0	9 (37.5) 17
Drug interrupted	1 (12.5) 1	1 (12.5) 1	1 (12.5) 4	3 (12.5) 6
Dose not changed	8 (100.0) 41	8 (100.0) 50	8 (100.0) 32	24 (100.0) 123
Not applicable	3 (37.5) 9	5 (62.5) 8	1 (12.5) 1	9 (37.5) 18
Events requiring additional data collection				
Injection site reaction	2 (25.0) 4	1 (12.5) 1	3 (37.5) 3	6 (25.0) 8
Accidental misadministration	1 (12.5) 1	2 (25.0) 2	0	3 (12.5) 3
Outcome				
Fatal	0	0	0	0
Not recovered/not resolved	4 (50.0) 4	1 (12.5) 1	0	5 (20.8) 5
Recovered/resolved with sequelae	1 (12.5) 1	0	0	1 (4.2) 1
Recovering/resolving	1 (12.5) 1	0	0	1 (4.2) 1
Recovered/resolved	7 (87.5) 50	8 (100.0) 70	8 (100.0) 37	23 (95.8) 157
Most common AEs by SOC (≥10% of participants)				
Metabolism and nutrition disorders	7 (87.5) 7	7 (87.5) 7	6 (75.0) 6	20 (83.3) 20
General disorders and administration site conditions	4 (50.0) 11	6 (75.0) 9	7 (87.5) 8	17 (70.8) 28
Gastrointestinal disorders	5 (62.5) 21	7 (87.5) 34	3 (37.5) 4	15 (62.5) 59
Nervous system disorders	3 (37.5) 3	4 (50.0) 6	2 (25.0) 2	9 (37.5) 11
Injury, poisoning, and procedural complications	3 (37.5) 3	3 (37.5) 3	2 (25.0) 2	8 (33.3) 8
Investigations	1 (12.5) 3	2 (25.0) 4	3 (37.5) 10	6 (25.0) 17

(Continues)

TABLE 3 (Continued)

	PYY1875 1.0 mg, semaglutide 2.4 mg	PYY1875 2.0 mg, semaglutide 2.4 mg	Placebo, semaglutide 2.4 mg	Total
Infections and infestations	1 (12.5) 1	3 (37.5) 3	0	4 (16.7) 4
Skin and s.c. tissue disorders	1 (12.5) 1	1 (12.5) 1	2 (25.0) 2	4 (16.7) 4
Psychiatric disorders	1 (12.5) 2	1 (12.5) 1	1 (12.5) 1	3 (12.5) 4

Note: Data are expressed as *n* (%) *E*, where *n* is the number of participants reporting an event, % is the percentage of participants reporting an event, and *E* is the number of events.
Abbreviations: AE, adverse event; SAS, safety analysis set; s.c., subcutaneous; SOC, system organ class; TEAE, treatment emergent adverse event.

semaglutide, from here on referred to as PYY1875-1.0 + semaglutide, PYY1875-2.0 + semaglutide, and placebo + semaglutide, respectively. Although 15 participants completed part 1, 9 participants (7 on PYY1875-2.0 + semaglutide and 2 on PYY1875-1.0 + semaglutide) discontinued the study product because of AEs. In part 2, 96 participants with obesity were included in part 2a to receive semaglutide for 32 weeks, of whom 83 participants were randomized in part 2b to receive either 1.0-mg ($n = 47$ participants) or 2.0-mg ($n = 8$) PYY1875 or placebo ($n = 28$) as an add-on to the ongoing semaglutide (Figure 3C,D). The 1.0-mg PYY1875 dose was investigated for safety and efficacy whereas the 2.0-mg dose was only investigated for safety. A total of 63 (75.9%) participants completed part 2, whereas 20 participants (14 on PYY1875-1.0 + semaglutide, 1 on PYY1875-2.0 + semaglutide, and 5 on placebo + semaglutide) discontinued the study product. In the PYY1875-1.0 + semaglutide group, 63.8% of participants (30) reached the target dose of 1.0 mg; however only 42.6% (20) were on the target dose at EOT. In the PYY1875-2.0 + semaglutide group, only 37.5% of participants (3) reached and stayed on the target dose of 2.0 mg at EOT. Baseline characteristics can be found in Table S5 (part 1), S6 (part 2a), and S7 (part 2b).

Safety and tolerability

Summary statistics for TEAEs are shown in Table 3 (part 1), Table S8 (part 2a), and Table 4 (part 2b). During part 1, the 1.0-mg PYY1875 dose escalation regimen appeared tolerable: Two of eight participants discontinued due to AEs (gastrointestinal, depression). However, the 2.0-mg regimen was not tolerated: Seven of eight participants discontinued due to gastrointestinal AEs between weeks 3 and 12. Overall, no clinically relevant changes were seen for vital signs, prostate-specific antigen, hormones, 24-h urine collection and urinalysis, or other biochemistry or hematology parameters based on change from baseline within treatment groups and compared with semaglutide alone.

During part 2a, four AEs led to treatment discontinuation. In part 2b, AEs leading to premature treatment discontinuation were more frequent with PYY1875-1.0 + semaglutide (21.3%) versus placebo + semaglutide (10.7%). One of eight participants (12.5%) discontinued treatment in the PYY1875-2.0 + semaglutide group. Discontinuations in both parts were predominantly due to gastrointestinal AEs, which occurred during dose escalation or after the full escalation period and appeared persistent. Two serious TEAEs were recorded in the PYY1875-1.0 + semaglutide group, but causality to treatment was deemed unlikely in both events. Severe events were more frequently reported with PYY1875-1.0 + semaglutide (15%) versus placebo + semaglutide (4%). Gastrointestinal AEs were the most frequent event type with 68% in the PYY1875-1.0 + semaglutide group versus 29% in the placebo + semaglutide group. There were no clinically relevant findings in other system organ classes or laboratory or other safety parameters, and there were no fatal events. Although the 1.0-mg dose of PYY1875 appeared safe, there were tolerability issues; only 30 out of 47 participants reached the target dose. No safety evaluation can be made for the 2.0-mg dose as only three participants reached the target dose.

PK analysis

In part 1, PK data for the PYY1875-1.0 + semaglutide group (Figure 4A) show a peak PYY1875 plasma concentration at day 88 (approximately 12.6 weeks). In part 2b (Figure 4B), a higher geometric mean plasma concentration of PYY1875 was observed with PYY1875-2.0 + semaglutide compared with PYY1875-1.0 + semaglutide. Peak concentration was observed at week 44 in the PYY1875-1.0 + semaglutide group and at week 46 in the PYY1875-2.0 + semaglutide group.

PD findings

PD endpoints were only assessed in part 2b and only in PYY1875-1.0 + semaglutide versus placebo + semaglutide. A total of 20 out of 47 participants (42.6%) in the PYY1875-1.0 + semaglutide group were on the target dose at EOT. Mean (SD) body weight for all randomized participants was 102.1 (14.4) kg at the beginning of the run-in period (week 0) and 87.5 (15.5) kg at baseline (week 32; Figure 4C). A modest treatment difference of −2.2 percentage points (95% CI: −4.2 to −0.1) or −2.2 kg (95% CI: −4.1 to −0.3) was found for PYY1875 1.0 mg versus placebo as an add-on to

TABLE 4 Phase 2 study, part 2b: TEAEs in the SAS.

	PYY1875 1.0 mg, semaglutide 2.4 mg	PYY1875 2.0 mg, semaglutide 2.4 mg	Placebo, semaglutide 2.4 mg	Total
Number of participants	47	8	28	83
Person years of observation	21.2	3.4	13.1	37.8
Events	43 (91.5) 220 *1036.8*	7 (87.5) 45 *1317.0*	19 (67.9) 56 *426.8*	69 (83.1) 321 *850.2*
Serious				
Yes	2 (4.3) 2 *9.4*	0	0	2 (2.4) 2 *5.3*
No	43 (91.5) 218 *1027.4*	7 (87.5) 45 *1317.0*	19 (67.9) 56 *426.8*	69 (83.1) 319 *844.9*
Severity				
Severe	7 (14.9) 8 *37.7*	0	1 (3.6) 1 *7.6*	8 (9.6) 9 *23.8*
Moderate	32 (68.1) 97 *457.2*	5 (62.5) 13 *380.5*	10 (35.7) 16 *121.9*	47 (56.6) 126 *333.7*
Mild	34 (72.3) 115 *542.0*	6 (75.0) 32 *936.5*	16 (57.1) 39 *297.2*	56 (67.5) 186 *492.6*
Relationship to semaglutide				
Probable	17 (36.2) 30 *141.4*	2 (25.0) 8 *234.1*	3 (10.7) 3 *22.9*	22 (26.5) 41 *108.6*
Possible	20 (42.6) 46 *216.8*	5 (62.5) 17 *497.5*	6 (21.4) 12 *91.5*	31 (37.3) 75 *198.6*
Unlikely	32 (68.1) 142 *669.2*	7 (87.5) 20 *585.3*	16 (57.1) 41 *312.4*	55 (66.3) 203 *537.6*
Missing	1 (2.1) 2 *9.4*	0	0	1 (1.2) 2 *5.3*
Relationship to PYY1875				
Probable	26 (55.3) 95 *447.7*	3 (37.5) 12 *351.2*	8 (28.6) 10 *76.2*	37 (44.6) 117 *309.9*
Possible	23 (48.9) 56 *263.9*	5 (62.5) 20 *585.3*	6 (21.4) 16 *121.9*	34 (41.0) 92 *243.7*
Unlikely	25 (53.2) 60 *282.8*	6 (75.0) 12 *351.2*	13 (46.4) 30 *228.6*	44 (53.0) 102 *270.1*
Missing	4 (8.5) 9 *42.4*	1 (12.5) 1 *29.3*	0	5 (6.0) 10 *26.5*
Action taken to semaglutide				
Drug interrupted	3 (6.4) 6 *28.3*	1 (12.5) 5 *146.3*	2 (7.1) 3 *22.9*	6 (7.2) 14 *37.1*
Drug withdrawn	4 (8.5) 9 *42.4*	1 (12.5) 4 *117.1*	1 (3.6) 1 *7.6*	6 (7.2) 14 *37.1*
Dose reduced	1 (2.1) 1 *4.7*	0	1 (3.6) 2 *15.2*	2 (2.4) 3 *8.0*
Dose increased	0	0	1 (3.6) 1 *7.6*	1 (1.2) 1 *2.7*
Dose not changed	42 (89.4) 199 *937.9*	6 (75.0) 31 *907.3*	19 (67.9) 44 *335.3*	67 (80.7) 274 *725.7*
Unknown	0	0	0	0
Not applicable	3 (6.4) 3 *14.1*	2 (25.0) 5 *146.3*	3 (10.7) 5 *38.1*	8 (9.6) 13 *34.4*
Missing	1 (2.1) 2 *9.4*	0	0	1 (1.2) 2 *5.3*
Action taken to PYY1875				
Drug interrupted	7 (14.9) 12 *56.6*	1 (12.5) 5 *146.3*	2 (7.1) 3 *22.9*	10 (12.0) 20 *53.0*
Drug withdrawn	8 (17.0) 15 *70.7*	1 (12.5) 4 *117.1*	1 (3.6) 1 *7.6*	10 (12.0) 20 *53.0*
Dose reduced	15 (31.9) 57 *268.6*	2 (25.0) 4 *117.1*	2 (7.1) 4 *30.5*	19 (22.9) 65 *172.2*
Dose increased	0	0	0	0
Dose not changed	37 (78.7) 124 *584.4*	6 (75.0) 26 *760.9*	18 (64.3) 43 *327.7*	61 (73.5) 193 *511.2*
Unknown	0	0	0	0
Not applicable	3 (6.4) 3 *14.1*	2 (25.0) 5 *146.3*	3 (10.7) 5 *38.1*	8 (9.6) 13 *34.4*
Missing	4 (8.5) 9 *42.4*	1 (12.5) 1 *29.3*	0	5 (6.0) 10 *26.5*
Outcome				
Fatal	0	0	0	0
Recovered/resolved	42 (89.4) 199 *937.9*	7 (87.5) 35 *1024.3*	18 (64.3) 39 *297.2*	67 (80.7) 273 *723.0*
Recovered/resolved with sequelae	1 (2.1) 1 *4.7*	0	0	1 (1.2) 1 *2.7*
Recovering/resolving	1 (2.1) 1 *4.7*	2 (25.0) 3 *87.8*	0	3 (3.6) 4 *10.6*
Not recovered/not resolved	14 (29.8) 19 *89.6*	2 (25.0) 7 *204.9*	7 (25.0) 17 *129.6*	23 (27.7) 43 *113.9*
Unknown	0	0	0	0

(Continues)

TABLE 4 (Continued)

	PYY1875 1.0 mg, semaglutide 2.4 mg	PYY1875 2.0 mg, semaglutide 2.4 mg	Placebo, semaglutide 2.4 mg	Total
Leading to premature treatment discontinuation	10 (21.3) 10 *47.1*	1 (12.5) 1 *29.3*	3 (10.7) 3 *22.9*	14 (16.9) 14 *37.1*
Most common AEs by SOC (≥10% of participants)				
Gastrointestinal disorders	32 (68.1) 124 *584.4*	6 (75.0) 26 *760.9*	8 (28.6) 10 *76.2*	46 (55.4) 160 *423.8*
Infections and infestations	15 (31.9) 17 *80.1*	1 (12.5) 1 *29.3*	6 (21.4) 6 *45.7*	22 (26.5) 24 *63.6*
Injury, poisoning, and procedural complications	11 (23.4) 12 *56.6*	1 (12.5) 1 *29.3*	6 (21.4) 8 *61.0*	18 (21.7) 21 *55.6*
General disorders and administration site conditions	5 (10.6) 7 *33.0*	3 (37.5) 6 *175.6*	4 (14.3) 5 *38.1*	12 (14.5) 18 *47.7*
Metabolism and nutrition disorders	7 (14.9) 8 *37.7*	2 (25.0) 3 *87.8*	3 (10.7) 5 *38.1*	12 (14.5) 16 *42.4*
Nervous system disorders	5 (10.6) 14 *66.0*	1 (12.5) 2 *58.5*	4 (14.3) 8 *61.0*	10 (12.0) 24 *63.6*
Investigations	5 (10.6) 7 *33.0*	0	4 (14.3) 6 *45.7*	9 (10.8) 13 *34.4*

Note: Data are expressed as *n* (%) *E* R, where *n* is the number of participants reporting an event, % is the percentage of participants reporting an event, *E* is the number of events, and R is the event rate per 100 years of observation time.
Abbreviations: AE, adverse event; SAS, safety analysis set; SOC, system organ class; TEAE, treatment emergent adverse event.

semaglutide 2.4 mg. After the average weight loss of 14.3%/14.6 kg during the run-in, change in body weight from baseline to EOT was −5.3%/−4.3 kg with PYY1875-1.0 + semaglutide versus −3.1%/−2.2 kg with placebo + semaglutide (Figure 4D).

However, no significant difference between PYY1875-1.0 + semaglutide and placebo + semaglutide was observed in waist circumference from baseline to EOT, although a trend of a more pronounced decrease could be seen for PYY1875-1.0 + semaglutide versus placebo + semaglutide (Figure 4E). Mean HbA1c decreased in a similar manner in the PYY1875-1.0 + semaglutide group and the placebo + semaglutide group (Figure 4F) during treatment and returned to baseline levels by EOS. Mean fasting plasma glucose (Figure 4G) and serum insulin levels (Figure 4H) appeared to be relatively stable in both groups from baseline to EOT as could be expected for individuals without diabetes. Total, HDL, and LDL cholesterol levels did not vary much during treatment in either group, whereas a slight trend toward a decreased EOT to baseline ratio could be seen for VLDL cholesterol, triglycerides, and free fatty acids with PYY1875-1.0 + semaglutide compared with placebo + semaglutide (Figure 4I).

DISCUSSION

The novel long-acting $PYY_{3\text{-}36}$ analogue PYY1875 was designed for weight management in obesity as a fixed-dose combination with semaglutide. Here, we have presented results from a DIO rat model as well as phase 1 and 2 clinical studies.

$PYY_{3\text{-}36}$ analogues have been popular targets for achieving weight loss and shown promising results in preclinical studies, both alone [28–30] and in combination with GLP-1 receptor agonists (GLP-1RAs) [31–33]. In this study, PYY1875 induced additional body weight loss in semaglutide-treated obese rats, exceeding results seen with high-dose semaglutide.

The findings in preclinical studies provided a strong rationale for advancing to clinical studies to evaluate the potential benefits of PYY1875 in humans. In the phase 1 study, all tested doses of PYY1875 alone and coadministered with semaglutide 0.25 mg were safe and tolerated in participants with overweight or obesity, and the PK properties supported once-weekly dosing. In the phase 2 study, PYY1875 was investigated in combination with semaglutide 2.4 mg for 16 weeks in participants with obesity after a 32-week semaglutide-only run-in period. Following an average of 14.3% body weight loss during the run-in, a modest treatment effect of PYY1875 1.0 mg versus placebo as an add-on to semaglutide was observed: −5.6% versus −3.1%, respectively. The higher 2.0-mg PYY1875 dose was not tolerated, mainly due to gastrointestinal-related AEs, which were also common with the 1.0-mg dose when added to semaglutide 2.4 mg using the escalation schedule applied here.

$PYY_{3\text{-}36}$ analogues have also previously been shown to cause gastrointestinal-related AEs, especially nausea. In a phase 1 study of 200 and 600 μg of intranasal $PYY_{3\text{-}36}$, a majority of participants receiving 600 μg discontinued treatment due to nausea and vomiting [34]. In a phase 1 study of PYY analogue Y14, dose-related gastrointestinal AEs were reported, but they were mild and rarely led to discontinuation, although it should be noted that planned higher doses were not given due to the emerging gastrointestinal AE profile [35].

The intranasal $PYY_{3\text{-}36}$ was concluded not to be efficacious in inducing weight loss in participants with obesity after 12 weeks of treatment based on −3.7-kg weight loss with a 200-μg dose versus −2.8 kg with placebo [34]. In the phase 1 Y14 study, participants given multiple doses of Y14 lost −2.9 to −3.6 kg more body weight than the placebo group ($p < 0.0001$) at 31 days from first dose [35].

PYY1875 was developed for use in combination with the GLP-1RA semaglutide (2.4 mg), which alone results in 14.9% weight loss over 68 weeks [36]. Increasing the well-known efficacy of GLP-1RAs in weight management by introducing dual or triple treatment regimens [37], either as combination therapies [15, 19, 38, 39] or as single-molecule dual

[40, 41] and tri-agonists [42], has been investigated in several clinical studies with promising results. Weight loss up to 17.1% over 20 weeks has been observed with the combination of the GLP-1RAs semaglutide and cagrilintide (2.4 mg of each) [38], 20.9% over 72 weeks with the dual GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptor agonist tirzepatide

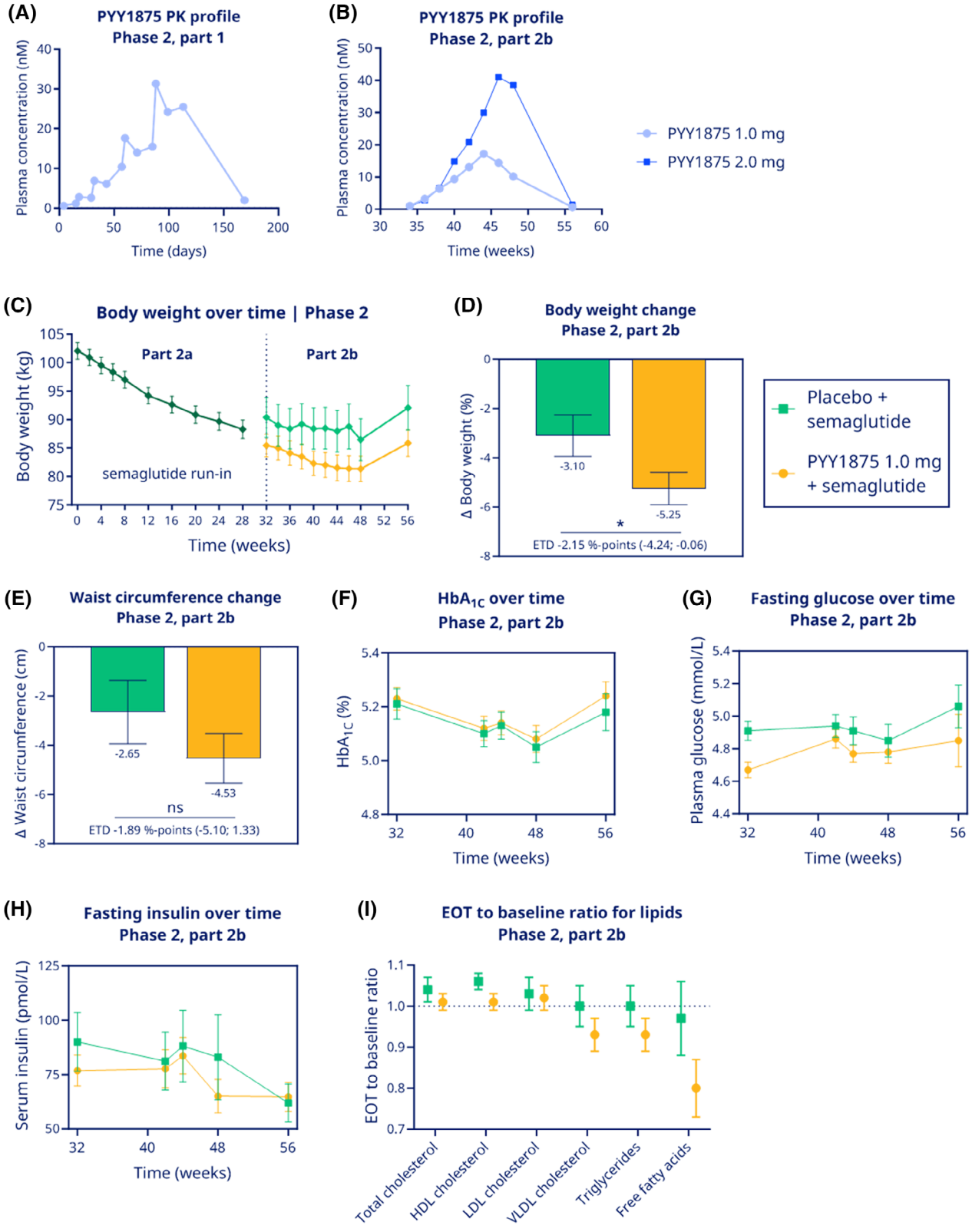


FIGURE 4 Legend on next page.

(15 mg) [40], and 24.2% over 48 weeks with the GLP-1/GIP/glucagon receptor tri-agonist retatrutide (12 mg) [42], all once-weekly treatments in individuals with overweight or obesity. The weight loss observed with PYY1875 1.0 mg over 16 weeks as an add-on to ongoing semaglutide was unfortunately lower than what is seen with other therapies complementing GLP-1 receptor agonism with additional pharmacotherapeutic targets, even considering that the participants had been treated with semaglutide for 32 weeks when the PYY1875 efficacy study started. Besides PYY1875, the Y_2 agonist BI 1820237 has also been investigated in clinical studies combined with the GLP-1RA liraglutide, but efficacy results are not available [43].

Generally, anti-obesity medications induce more relative weight loss in DIO rodents than in humans [18], as also seen here with PYY1875. Issues with tolerability hampered higher PYY1875 dosing, which could have improved efficacy. It is possible that a gentler dose escalation regimen to mitigate the AEs would have enabled PD endpoints to be studied with the 2.0-mg dose. It should also be noted that this study focused on individuals without diabetes, and PYY1875 treatment could potentially have additional benefits in individuals with impaired glucose metabolism. Future research may focus on optimizing the dosing regimen or exploring alternative pharmacotherapeutic combinations to enhance the therapeutic potential of PYY1875 while minimizing adverse effects.

Limitations of the studies

The clinical studies had common phase 1/2 limitations, such as small sample size and short duration. As the clinical study participants did not have diabetes, the data on glucose metabolism are not applicable to individuals with impaired glucose metabolism.

CONCLUSION

Although PYY1875 demonstrated potential in preclinical studies and showed modest efficacy in clinical studies, its tolerability issues, particularly gastrointestinal-related AEs, limit its clinical utility as an add-on therapy to semaglutide for weight management in obesity.O

AUTHOR CONTRIBUTIONS

Data were analyzed by the sponsor. All authors contributed to interpretation of data as well as writing, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors thank all participants, investigators, and site staff who were involved in the conduct of the clinical studies.

FUNDING INFORMATION

The study was sponsored by Novo Nordisk A/S. The sponsor was involved in the study design, data collection, data review, data analysis, and drafting of the report.

CONFLICT OF INTEREST STATEMENT

Birgitte S. Wulff is a former employee and shareholder of Novo Nordisk A/S. Adam Paul Chambers is an employee and shareholder of Novo Nordisk A/S. Cynthia Karenina Osorto Contreras is an employee and shareholder of Novo Nordisk A/S. Katrine Kirkeby is an employee and shareholder of Novo Nordisk A/S. Anders Rasmussen Rinnov is an employee and shareholder of Novo Nordisk A/S. Riia K. Sustarsic is an employee of Novo Nordisk A/S. Søren Østergaard is an employee and shareholder of Novo Nordisk A/S. John E. Laabs is a former employee of Celerion, Inc. Patrick M. O'Neil has received research support and consulting fees from Novo Nordisk A/S, Eli Lilly, and Epitomee Medical and nonpromotional speaking fees from Robard Corp.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifiers NCT03707990 and NCT04969939.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FIGURE 4 Results from phase 2 study. (A) Geometric mean PYY1875 plasma concentration in part 1 for the PYY1875-1.0 + semaglutide group (for the six treatment completers). (B) Geometric mean PYY1875 plasma concentration in part 2b for the PYY1875-1.0 + semaglutide and PYY1875-2.0 + semaglutide groups (FAS with 39–46 and 5–8 participants contributing to PK data, respectively). (C) Mean observed body weight over part 2a and part 2b. (D) Body weight change (%) from baseline to EOT (part 2b). (E) Waist circumference change (cm) from baseline to EOT (part 2b). (F) HbA1c (%) over time (part 2b). (G) Fasting plasma glucose (mmol/L) over time (part 2b). (H) Fasting serum insulin (pmol/L) over time (part 2b). (I) EOT to baseline ratio for cholesterol (total, HDL, LDL, and VLDL), triglycerides, and free fatty acids (part 2b). In panels A and B, geometric means are plotted. In panels C and F–H, observed mean and SEM are plotted. In panels D and E, EOT (week 48) data have been analyzed using an ANCOVA model with randomized treatment as factors and baseline body weight (kg) as covariate. Missing observations were imputed based on an RSMI model. Estimated change from baseline and SEM are plotted, and ETD with 95% CI is included in the graph. In panel I, EOT (week 48) data have been analyzed using an ANCOVA model with randomized treatment as factors and baseline body weight (kg) as covariate. Missing observations were imputed based on an RSMI model. Estimated ratio to baseline and SEM are plotted. Treatment ratios are not significant. $^*p < 0.05$. EOS, end of study; EOT, end of treatment; ETD, estimated treatment difference; FAS, full analysis set; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low- density lipoprotein; ns, nonsignificant; PK, pharmacokinetic; RSMI, retrieved subjects-based multiple imputation; VLDL, very low-density lipoprotein. [Color figure can be viewed at wileyonlinelibrary.com]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wulff BS, Chambers AP, Osorto Contreras CK, et al. Long-acting PYY_{3-36} analogue with semaglutide for obesity: from preclinical assessment through randomized clinical studies. *Obesity (Silver Spring)*. 2025;1-18. doi:10.1002/oby.24329