

RESEARCH MONOGRAPH . COMPOUND PROFILE

Petrelintide

A 36-amino-acid acylated peptide engineered from human amylin with a lactam bridge, N-methylations, and C20 diacid lipidation enabling neutral-pH stability, albumin-mediated half-life extension to approximately 10 days, and once-weekly dosing for obesity and weight management.

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ABSTRACT

Petrelintide (ZP-8396) is a long-acting, subcutaneously administered analog of human amylin developed by Zealand Pharma A/S (Soborg, Denmark) as a potential foundational therapy for chronic weight management in adults with overweight and obesity. The compound is a 36-amino-acid acylated peptide bearing a lactam bridge replacement of the native Cys2-Cys7 disulfide bond, N-methylations at Gly24 and Ile26 to prevent amyloid fibrillation, strategic asparagine deletions and substitutions to eliminate deamidation-prone residues, a C-terminal hydroxyproline substitution for enhanced receptor potency, and an N-terminal C20 diacid lipidation via a gamma-glutamic acid linker that confers reversible albumin binding and a human terminal half-life of approximately 10 days, supporting convenient once-weekly dosing. Petrelintide exhibits potent balanced agonism at the amylin-3 receptor (AMY3R, EC₅₀ 0.33 nM) and the calcitonin receptor (CTR, EC₅₀ 0.32 nM) in cAMP accumulation assays, classifying it as a dual amylin and calcitonin receptor agonist (DACRA). In diet-induced obese rat models, repeated dosing produces dose-dependent reductions in food intake and body weight with preferential fat mass loss and relative preservation of lean mass. Clinical development has progressed rapidly. A first-in-human Phase 1 single ascending dose trial (NCT05096598) established safety and tolerability at subcutaneous doses of 0.04 to 2.4 mg, with a human half-life supporting weekly administration. A Phase 1b multiple ascending dose trial in 48 participants with overweight or obesity demonstrated mean body weight reductions of 4.8% (2.4 mg), 8.6% (4.8 mg), and 8.3% (9.0 mg) versus 1.7% with placebo after 16

weekly doses, with no serious or severe adverse events and gastrointestinal tolerability substantially superior to the adverse-event profiles reported for GLP-1 receptor agonist monotherapy at comparable weight-loss magnitudes. The Phase 2 ZUPREME-1 trial (NCT06662539) in 493 adults with obesity met its primary endpoint across all five dose arms, achieving up to 10.7% mean body weight reduction at 42 weeks with placebo-like tolerability, zero vomiting at the maximally effective dose, and discontinuation rates due to adverse events comparable to placebo (4.8% versus 4.9%). In March 2025, Roche entered an exclusive global collaboration and licensing agreement with Zealand Pharma valued at up to 5.3 billion US dollars to co-develop and co-commercialize petrelintide as monotherapy and in fixed-dose combination with CT-388, a dual GLP-1/GIP receptor agonist. Phase 3 initiation for chronic weight management is planned for the second half of 2026. Petrelintide is an investigational compound; its safety and efficacy have not been established by any regulatory authority. This monograph reviews the peptide chemistry, receptor pharmacology, preclinical and clinical evidence base, pharmacokinetic profile, and comparative positioning of petrelintide within the amylin receptor agonist landscape, grounded in the primary literature through May 2026. Investigators should treat all data as preliminary pending registration-quality Phase 3 results and regulatory evaluation.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Petrelintide (INN #12663, WHO recommended) [1].

Development code: ZP-8396 (Zealand Pharma internal designation). The development code appears in ClinicalTrials.gov registrations and early-phase publications [2].

Chemical Abstracts Service registry number: 2766385-23-1 [3].

Unique Ingredient Identifier (UNII): D78KBY7BRU (FDA Substance Registration System) [3].

National Cancer Institute Thesaurus code: C203201 [3].

PubChem Compound Identifiers: CID 172915807 (petrelintide), CID 176451455 (petrelintide ZP8396 entry) [4].

IUPHAR/BPS Guide to Pharmacology Ligand ID: 13804 [5].

InChIKey: TVOIUFVYEVVHCS-HJODGROVSA-N [5].

1.2 Structural class and chemistry

Petrelintide is a 36-amino-acid synthetic peptide analog of human amylin (islet amyloid polypeptide, IAPP), engineered for chemical stability at neutral pH, resistance to amyloid fibrillation, and extended circulating half-life through reversible albumin binding [1]. The compound belongs to the structural class of long-acting lipidated amylin analogs and is pharmacologically classified as a dual amylin and calcitonin receptor agonist (DACRA) [5, 6].

Molecular formula: C₁₈₅H₃₀₅N₄₉O₆₁ (PubChem CID 172915807) [4]. An alternate molecular formula of C₁₈₄H₃₀₂N₄₈O₆₁ is listed in some databases for the free peptide without acetate counterion [4].

Molecular weight: Approximately 4191.7 daltons (GtoPdb) [5].

Physical properties: The peptide is formulated as a clear aqueous solution for subcutaneous injection. Petrelintide is soluble in aqueous buffers across a pH range of 6.1 to 7.4 in histidine, phosphate, and Tris buffer systems [1]. The isoelectric point (pI) is 4.0, contributing to favorable solubility at physiological pH and correlation with extended circulating half-life [1].

Particle size: 1.8 to 4.0 nm by dynamic light scattering (Z-average), consistent with monomeric or low-oligomeric peptide in solution without fibrillation [1].

1.3 Structural modifications from human amylin

Native human amylin is a 37-amino-acid peptide with an intramolecular disulfide bridge between Cys2 and Cys7 and an amidated C-terminus, co-secreted with insulin by pancreatic beta-cells [6]. Petrelintide incorporates the following modifications to achieve stability, potency, and extended pharmacokinetics [1]:

Disulfide replacement: The native Cys2-Cys7 disulfide bond is replaced with a 6-atom lactam bridge between Asp2 and Lys7. The lactam is positioned with the amide bond closer to position 2, which is critical for retention of receptor activity (translocation to position 7 reduced potency 260-fold, from EC₅₀ 0.38 nM to 88 nM) [1]. The lactam eliminates the oxidative lability of the disulfide and prevents disulfide-mediated dimerization (0% dimers at 14 days versus 11% for the disulfide parent) [1].

Fibrillation prevention: N-methylation of Gly24 and Ile26 disrupts the beta-sheet hydrogen bonding network that drives amyloid fibrillation of native human amylin [1]. Combined with other substitutions, these modifications eliminate fibrillation at pH 6.1 to 7.4 under accelerated stability conditions (40 degrees Celsius, 1 month) [1].

Deamidation prevention: Human amylin contains six asparagine residues (positions 3, 14, 21, 22, 31, 35) susceptible to deamidation. Petrelintide eliminates deamidation sites through: Asn3 to Gly substitution; Asn14 to adipic acid (Aad) substitution; deletion of Asn21 and Asn22 (reducing the peptide from 37 to 35 residues at this segment); Asn31 to Glu substitution [1]. Peptides with three or fewer asparagine residues demonstrated mean stability greater than 90% after 7 days at 40 degrees Celsius and pH 7.5, compared to less than 40% for unmodified human amylin [1].

Potency optimization: C-terminal Tyr37 is replaced with hydroxyproline, producing a 3- to 4-fold increase in AMY3R potency and approximately 7-fold increase in CTR potency [1]. Additional substitutions include Ala1 to Arg, Gln10 to Glu, His17 to Gln, and His18 to Arg [1].

Half-life extension: An N-terminal C20 diacid lipidation with a gamma-glutamic acid linker confers extensive but reversible albumin binding in plasma, reducing renal clearance and extending the circulating half-life from minutes (native amylin) to approximately 10 days in humans [1, 2, 7].

1.4 Stability and coformulation

Petrelintide demonstrates less than 3% total chemical degradation and less than or equal to 0.2% covalent oligomer formation under accelerated conditions (pH 6.1 to 7.4, 40 degrees Celsius, 1 month) across histidine, phosphate, and Tris buffer systems [1]. No fibrillation was detected under any tested condition [1].

Coformulation studies with semaglutide (1 mg/mL petrelintide plus 1 mg/mL semaglutide in Tris/NaCl at pH 6.7 or phosphate/propylene glycol/phenol at pH 7.4) demonstrated no substantial effect on degradation rates or aggregation over 4 weeks at 40 degrees Celsius (relative degradation rate 1.0 to 1.1) [1]. This coformulation compatibility is a deliberate design feature enabling potential fixed-dose combination products with incretin-class peptides.

2. Abstract

Petrelintide (ZP-8396) is a 36-amino-acid acylated peptide analog of human amylin developed by Zealand Pharma A/S as a once-weekly subcutaneous therapy for chronic weight management. The compound addresses the three principal limitations of pramlintide (the only previously approved amylin analog): it is chemically stable and non-fibrillating at neutral pH, enabling coformulation with other peptide therapeutics; it has a terminal half-life of approximately 10 days in humans, supporting once-weekly rather than three-times-daily dosing; and it is a potent, balanced dual amylin and calcitonin receptor agonist (DACRA) with subnanomolar EC₅₀ values at both AMY3R and CTR [1, 2].

In the Phase 1b multiple ascending dose trial, 48 participants receiving 16 weekly doses achieved mean body weight reductions of up to 8.6% (4.8 mg maintenance dose) versus 1.7% with placebo, with no serious or severe adverse events and gastrointestinal adverse event rates that differed minimally from placebo [7, 12]. The Phase 2 ZUPREME-1 trial (NCT06662539) in 493 adults with obesity extended these findings, demonstrating 10.7% mean body weight reduction at the maximally effective dose at 42 weeks, with zero vomiting events at that dose, and overall discontinuation rates due to adverse events comparable to placebo (4.8% versus 4.9%) [13]. The tolerability profile, described as "placebo-like" by the sponsor, is sharply differentiated from the gastrointestinal adverse event burden reported for GLP-1 receptor agonists at comparable weight-loss efficacy.

The Roche collaboration (March 2025, valued at up to 5.3 billion US dollars) positions petrelintide for Phase 3 development as both monotherapy and in fixed-dose combination with CT-388, a dual GLP-1/GIP receptor agonist [14]. The compound is investigational; all data presented in this monograph derive from early-phase clinical trials and preclinical studies. Investigators should treat reported efficacy and tolerability as requiring confirmation in Phase 3.

3. Discovery and Development History

3.1 Origin and rationale

Petrelintide was developed at Zealand Pharma A/S (Soborg, Denmark), a biotechnology company specializing in peptide therapeutics, with initial medicinal chemistry collaboration from Boehringer Ingelheim [1]. The compound was designed to address the three principal limitations of pramlintide, the only previously approved amylin analog: requirement for acidic pH formulation (pH 4.0) due to fibrillation at neutral pH, short circulating half-life requiring three-times-daily injection, and inability to be coformulated with other peptide therapeutics [1, 8].

The rationale for amylin-based obesity pharmacotherapy rests on amylin's physiological role as a postprandial satiety hormone. Native amylin is co-secreted with insulin from pancreatic beta-cells after nutrient ingestion and acts centrally, primarily at the area postrema and nucleus of the solitary tract, to promote meal-ending satiation, delay gastric emptying, suppress glucagon secretion, and increase energy expenditure [6, 9]. Preclinical and clinical evidence had demonstrated that amylin receptor activation produces body weight reduction predominantly through fat mass loss with relative preservation of lean mass, a profile differentiated from caloric restriction and potentially from GLP-1 receptor agonist monotherapy [6, 10].

3.2 Medicinal chemistry development

The development of petrelintide proceeded through systematic optimization of chemical stability while retaining in vitro and in vivo potency [1]. Key milestones in the medicinal chemistry program included:

First, identification that N-methylation of Gly24 and Ile26 reduced but did not eliminate fibrillation at neutral pH [1]. Second, discovery that reducing the number of asparagine residues to three or fewer (through deletion or substitution) was required for acceptable chemical stability (greater than 90% after 7 days at 40 degrees Celsius) [1]. Third, replacement of the disulfide bridge with a lactam eliminated oxidative dimerization while preserving receptor potency, provided the lactam ring size was 6 to 8 atoms and the amide bond was positioned near the N-terminal residue of the bridge [1]. Fourth, C-terminal hydroxyproline substitution at position

37 enhanced potency at both AMY3R and CTR [1]. Fifth, C20 diacid lipidation via gamma-glutamic acid linker achieved a pI of 4.0 and circulating half-life greater than 30 hours in rats, with the lower pI correlating with longer half-lives across the peptide series [1].

The final candidate (designated peptide 40 in the medicinal chemistry series) integrated all modifications and demonstrated: EC₅₀ 0.33 nM at AMY3R, EC₅₀ 0.32 nM at CTR, 97% chemical stability at 14 days accelerated conditions, 0% dimerization, no fibrillation at neutral pH, rat half-life of 33.8 hours, and dose-dependent food intake reduction and body weight loss in lean and obese rodent models [1].

3.3 Clinical development timeline

The clinical program was initiated in October 2021 with a first-in-human Phase 1 single ascending dose study (NCT05096598) in healthy participants, evaluating subcutaneous doses of 0.04 to 2.4 mg and a single intravenous dose of 0.35 mg [2, 11]. The study completed in January 2023 and confirmed safety, tolerability, and pharmacokinetic properties consistent with once-weekly dosing [2].

A Phase 1 multiple ascending dose study (NCT05613387) followed, with topline results from the 16-week treatment period (Part 2) reported on June 20, 2024. The study demonstrated clinically meaningful weight reductions of up to 8.6% with favorable tolerability, generating substantial industry and investor attention [7, 12].

The Phase 2 ZUPREME-1 trial (NCT06662539) was initiated in December 2024, enrolling 493 participants across 33 sites in the United States, Poland, and Romania. Topline results reported on March 5, 2026, demonstrated up to 10.7% body weight reduction at 42 weeks with placebo-like tolerability [13].

A second Phase 2 trial, ZUPREME-2, evaluating petrelintide in adults with overweight or obesity and type 2 diabetes, is expected to report topline results in the second half of 2026 [13].

3.4 Strategic partnership

On March 12, 2025, Roche entered an exclusive global collaboration and licensing agreement with Zealand Pharma for petrelintide and combination products [14]. The deal is valued at up to 5.3 billion US dollars: 1.65 billion in upfront payments (1.4 billion at closing plus 250 million over the first two anniversaries), 1.2 billion in

development milestones primarily tied to Phase 3 initiation, and 2.4 billion in sales-based milestones [14]. The agreement provides for 50/50 profit and loss sharing in the United States and Europe, tiered double-digit to high-teens royalties in the rest of world, and joint co-development of petrelintide monotherapy and a fixed-dose combination with CT-388, Roche's dual GLP-1/GIP receptor agonist [14].

Phase 3 initiation for petrelintide monotherapy in chronic weight management is planned for the second half of 2026 [13, 14].

4. Molecular Pharmacology

4.1 Amylin receptor biology

The amylin receptor system comprises heterodimeric complexes of the calcitonin receptor (CTR) with receptor activity-modifying proteins (RAMPs). Three amylin receptor subtypes are defined: AMY1R (CTR plus RAMP1), AMY2R (CTR plus RAMP2), and AMY3R (CTR plus RAMP3) [6, 9]. These receptor complexes have distinct pharmacological profiles, tissue distributions, and signaling properties. The CTR alone also responds to amylin at suprananomolar concentrations [6]. The receptors are located in satiety-regulating brain regions (hypothalamus, area postrema, nucleus tractus solitarius, lateral parabrachial nucleus) and in peripheral tissues including liver, gastric fundus, duodenum, kidney, and bone [6, 9].

Receptor signaling proceeds primarily through Gs-coupled cAMP accumulation, with additional engagement of Gq and beta-arrestin pathways depending on receptor subtype and cellular context [6]. The area postrema, a circumventricular organ lacking a complete blood-brain barrier, is the primary site of action for circulating amylin and amylin analogs acting as satiety signals [9, 15].

4.2 Petrelintide receptor binding and functional activity

Petrelintide was characterized in COS7 cells stably coexpressing human CTR with RAMP3 (for AMY3R) or CTR alone (for calcitonin receptor), using a cAMP accumulation assay (AlphaScreen cAMP Assay kit) [1].

AMY3R agonism: Petrelintide EC₅₀ = 0.33 nM (pEC₅₀ 9.48), compared to human amylin EC₅₀ = 0.51 nM (pEC₅₀ 9.29) [1]. The compound is thus approximately 1.5-fold more potent than the native hormone at this receptor subtype.

CTR agonism: Petrelintide EC₅₀ = 0.32 nM (pEC₅₀ 9.50), compared to human calcitonin EC₅₀ = 0.056 nM (pEC₅₀ 10.25) and human amylin EC₅₀ = 3.5 nM (pEC₅₀ 8.46) [1]. Petrelintide is approximately 11-fold more potent than native amylin at the calcitonin receptor, though approximately 6-fold less potent than the cognate calcitonin ligand.

This "balanced" potency at both AMY3R and CTR defines petrelintide's pharmacological classification as a dual amylin and calcitonin receptor agonist (DACRA) [5, 6]. The balanced profile contrasts with AMY1R-selective agents such as eloralintide and with the non-selective CTR/AMY receptor profile of cagrilintide [8, 15].

4.3 Structure-activity relationships

The medicinal chemistry campaign that produced petrelintide systematically defined the structural requirements for receptor activity within the modified amylin scaffold [1]:

Lactam bridge geometry: A 6-atom lactam bridge between Asp2 and Lys7 with the amide bond positioned closer to position 2 retains full AMY3R potency (EC₅₀ 0.38 nM for the initial lactam peptide 18) [1]. Translocation of the amide bond to position 7 within the same 6-atom bridge abolished activity (EC₅₀ 88 nM, a 230-fold loss) [1]. A 4-atom lactam was entirely inactive (EC₅₀ greater than 10 micromolar) [1].

C-terminal residue: Substitution of native Tyr37 with hydroxyproline increased AMY3R potency 3- to 4-fold and CTR potency approximately 7-fold [1]. Proline at the same position produced the AMY3R improvement but not the CTR enhancement.

Asparagine deletion at positions 21-22: Deletion of both Asn21 and Asn22 maintained full potency (EC₅₀ 0.19 nM versus 0.25 nM for the parent with these residues present), establishing that these positions are dispensable for receptor activation [1].

4.4 Mechanism of action for weight loss

Petrelintide's weight-reducing activity is mediated through central amylin receptor activation, primarily at the area postrema in the caudal hindbrain [6, 9, 15]. The physiological and pharmacological consequences include:

Satiety promotion: Activation of amylin receptors in the area postrema and nucleus of the solitary tract promotes meal-ending satiation and dose-dependently reduces meal size [6, 9]. The effect is on homeostatic and hedonic eating pathways.

Gastric emptying delay: Direct action on amylin receptors slows gastric emptying, delaying nutrient inflow to the small intestine and prolonging postprandial satiety signals [6, 9].

Glucagon suppression: Amylin receptor activation potently suppresses meal-induced glucagon secretion at physiologically relevant concentrations, reducing postprandial glucose excursions through inhibition of hepatic gluconeogenesis [6, 9].

Energy expenditure: Amylin increases energy expenditure independently of the area postrema, possibly through increased sympathetic nervous system activity [6]. This mechanism may contribute to the preferential fat mass loss observed with amylin analogs.

Leptin sensitization: Petrelintide has been reported to restore leptin sensitivity in the brain, potentially amplifying endogenous satiety signaling [7].

The calcitonin receptor component of petrelintide's balanced DACRA profile may contribute additional weight-reducing activity. Recent evidence from Carvas et al. (2025) demonstrated that cagrilintide (also a CTR/AMY receptor agonist) lowers body weight through a mechanism dependent on the presence of AMY1R and AMY3R, with area postrema neuronal activation reduced by 57% in RAMP1/3 knockout mice compared to wild-type [15]. The role of direct CTR agonism (independent of RAMP-modified receptors) in petrelintide's efficacy has not been formally dissected.

4.5 Body composition effects

Preclinical evidence and the physiological profile of amylin receptor activation indicate that amylin-mediated weight reduction produces preferential reduction of fat mass with relative preservation of lean mass [6, 10, 15]. In the Carvas et al. (2025) study of cagrilintide in diet-induced obese mice, treatment lowered body weight by acting on fat depots while maintaining lean mass, with plasma leptin decreasing 2-fold (suggesting fat mass reduction) [15]. The Phase 2 ZUPREME-1 trial of petrelintide included MRI-measured body composition as an exploratory endpoint at week 42; specific results have not yet been reported in the topline announcement [13].

5. Pharmacokinetics and Routes of Administration

5.1 Preclinical pharmacokinetics

Pharmacokinetic studies in lean male Sprague-Dawley rats following a single subcutaneous dose of 30 nmol/kg demonstrated [1]:

- Terminal half-life: 33.8 hours
- Time to maximum concentration (T_{max}): approximately 24 hours
- Maximum plasma concentration (C_{max}): approximately 2-fold higher than the disulfide-bridge parent peptide (peptide 37, half-life 39.5 hours)

The extended rat half-life is attributable to the C20 diacid lipidation, which mediates extensive but reversible albumin binding, reducing renal clearance [1]. Among the peptide series evaluated, isoelectric points below 5.0 consistently correlated with circulating half-lives exceeding 30 hours, while peptides with pI above 5.0 demonstrated half-lives typically below 30 hours [1].

5.2 Human pharmacokinetics

Human pharmacokinetic data derive from the Phase 1 SAD and MAD trials (NCT05096598 and NCT05613387) and are reported in the Braendholt Olsen et al. (2025) publication [2]:

- **Terminal half-life:** Approximately 10 days (240 hours), supporting once-weekly subcutaneous dosing [2, 7]
- **Subcutaneous bioavailability:** 85% [7]
- **Dose proportionality:** C_{max} and AUC at steady state demonstrated dose-proportional pharmacokinetics across the 0.6 to 9.0 mg dose range [2, 7]
- **Within-dose variability:** Low, consistent with predictable exposure at fixed weekly doses [7]

The approximately 7-fold increase in human half-life relative to the rat (240 hours versus 34 hours) is consistent with established interspecies allometric scaling of albumin-bound peptides, reflecting greater albumin binding capacity and slower albumin turnover in humans [1, 2].

5.3 Route of administration and dosing

Petrelintide is administered as a once-weekly subcutaneous injection [2, 7, 13]. The clinical dose escalation strategy in Phase 1b employed bi-weekly titration, with maintenance doses of 2.4 mg, 4.8 mg, and 9.0 mg evaluated [7, 12]. In Phase 2 (ZUPREME-1), five dose arms were studied with dose escalation every fourth week over up to 16 weeks, followed by maintenance dosing until week 42 [13].

The subcutaneous formulation is prepared in aqueous buffer at approximately neutral pH (6.1 to 7.4), distinct from the acidic (pH 4.0) formulation required for pramlintide [1, 8]. The neutral-pH stability enables potential coformulation with other peptide therapeutics that require neutral pH, including GLP-1 receptor agonists [1].

5.4 Metabolism and elimination

Petrelintide, as a peptide therapeutic, is expected to be cleared through proteolytic degradation and renal filtration rather than through hepatic cytochrome P450-mediated biotransformation [6]. The C20 diacid lipidation confers extensive albumin binding, which reduces renal clearance and is the principal mechanism of half-life extension [1]. Formal metabolite identification studies have not been published. The contribution of renal versus proteolytic clearance pathways is under investigation in the dedicated renal impairment pharmacokinetic study (NCT07076030) [16].

The low isoelectric point (pI 4.0) of petrelintide contributes to its extended pharmacokinetic profile [1]. Across the peptide series evaluated during development, peptides with pI below 5.0 consistently achieved circulating half-lives exceeding 30 hours in rats, while peptides with pI above 5.0 showed half-lives below 30 hours [1]. This correlation suggests that the net negative charge at physiological pH enhances albumin binding affinity or reduces non-specific tissue uptake.

5.5 Special populations

A dedicated pharmacokinetic study in participants with impaired renal function (NCT07076030) is registered and evaluating whether petrelintide exposure differs from that in participants with normal kidney function [16]. An additional study (NCT07338214) is evaluating pharmacokinetics across different drug product concentrations [17]. Formal studies of hepatic impairment, age, sex, and ethnicity effects on pharmacokinetics have not been published as of the monograph date, though the Phase 2 trial noted that female participants lost considerably more weight than male participants, which may reflect sex-based pharmacokinetic or pharmacodynamic differences [13].

6. Preclinical Pharmacology

6.1 Acute pharmacodynamic effects in lean rats

In lean male Sprague-Dawley rats, a single subcutaneous dose of petrelintide (peptide 40) at 30 nmol/kg produced [1]:

- Food intake at 24 hours: 70.8 plus or minus 1.6% of baseline (approximately 29% reduction)
- Body weight loss at 96 hours: 9.9 plus or minus 1.2%

For comparison, the disulfide-bridge parent peptide (peptide 37) at the same dose produced 71.8% baseline food intake and 8.3% body weight loss, indicating that petrelintide retained comparable in vivo efficacy despite the structural modifications required for stability [1].

6.2 Chronic efficacy in diet-induced obese rats

Petrelintide was evaluated in a diet-induced obese (DIO) rat model with repeated subcutaneous dosing every 48 hours for 20 days at doses of 1, 3, 10, and 15 nmol/kg [1]:

Food intake effects:

- Vehicle group: cumulative food intake of 390 grams per rat over 20 days
- 15 nmol/kg group: cumulative food intake of 298 grams per rat (23.6% reduction versus vehicle)
- Significant differences in daily food intake emerged from day 4 onward at doses of 3 nmol/kg and above [1]

Body weight effects:

- Vehicle: +16.9% body weight increase by day 20
- 3 nmol/kg: +8.7% increase (approximately 49% attenuation of weight gain)
- 10 nmol/kg: +3.8% increase (approximately 78% attenuation)
- 15 nmol/kg: +4.4% increase (approximately 74% attenuation) [1]

The plateau of weight effect between 10 and 15 nmol/kg suggests a ceiling of efficacy in this model at supratherapeutic receptor occupancy, consistent with the clinical observation that the 4.8 mg and 9.0 mg Phase 1b doses produced similar weight loss (8.6% and 8.3%, respectively) [1, 12].

6.3 Dose-response and efficacy ceiling

The DIO rat data reveal an apparent efficacy ceiling between 10 and 15 nmol/kg (body weight gain attenuation of 78% and 74% respectively, not statistically different), despite continued dose-dependent food intake reduction [1]. This pattern translates to the human Phase 1b observation that 4.8 mg and 9.0 mg produced nearly identical weight loss (8.6% versus 8.3%), suggesting that maximal amylin receptor-mediated satiety may be achieved below the highest tested doses [1, 12]. The implication for clinical development is that dose optimization above a ceiling provides no additional efficacy benefit while potentially increasing adverse event exposure; the Phase 2 ZUPREME-1 trial design with five dose arms was intended to identify this ceiling precisely [13].

6.4 Body composition

The amylin-mediated mechanism of weight loss in preclinical models produces preferential fat mass reduction with relative preservation of lean mass [6, 10]. The eloralintide DIO rat data (a structurally distinct long-acting amylin analog) reported that approximately 80 to 86% of weight loss was from fat mass [8]. Direct body composition measurements for petrelintide in DIO models have not been separately published in the primary literature, though the Zealand Pharma clinical characterization describes "potential for preservation of lean muscle" as a differentiated feature of the amylin mechanism relative to GLP-1 receptor agonist monotherapy [12, 13].

6.5 Comparison to other long-acting amylin analogs in preclinical models

In the same DIO rat model, eloralintide (LY3841136, an AMY1R-selective long-acting analog from Eli Lilly) at 100 nmol/kg every 3 days produced 12.3% weight reduction with 80 to 86% of loss from fat mass [8]. Eloralintide also demonstrated significantly less conditioned taste aversion than cagrilintide (ED₅₀ 8.9 versus 4.2

nmol/kg), suggesting that receptor selectivity may influence tolerability [8]. Direct preclinical head-to-head comparisons of petrelintide with cagrilintide or eloralintide in the same study have not been published.

7. Clinical Evidence Base

The following summarizes the clinical evidence base for petrelintide through May 2026. Petrelintide is an investigational compound whose safety and efficacy have not been evaluated or approved by any regulatory authority. All clinical data are from sponsor-conducted trials and topline announcements pending peer-reviewed full publication of some datasets.

7.1 Phase 1 single ascending dose study (NCT05096598)

The first-in-human study was a randomized, double-blind, placebo-controlled, single ascending dose trial in healthy participants evaluating subcutaneous doses of 0.04 to 2.4 mg and a single intravenous dose of 0.35 mg [2, 11]. The trial was conducted at a single center, initiated in October 2021, and completed in January 2023 [11].

Petrelintide was well tolerated at all doses, with no serious or severe treatment-emergent adverse events [2, 7]. The most common adverse events were gastrointestinal disorders, the majority mild [2]. Pharmacokinetic analysis confirmed a terminal half-life of approximately 10 days, validating the once-weekly dosing hypothesis derived from the rat pharmacokinetic data and interspecies allometric scaling [2, 7].

7.2 Phase 1b multiple ascending dose study (NCT05613387)

A randomized, double-blind, placebo-controlled, multiple ascending dose trial enrolled 48 participants (approximately 79% male, median age 49 years, median baseline BMI 29.9 kg/m², median body weight 92 kg) randomized 3:1 to petrelintide or placebo [7, 12]. Participants received 16 weekly subcutaneous doses with bi-weekly up-titration across three cohorts targeting maintenance doses of 2.4 mg (12 weeks at maintenance), 4.8 mg (8 weeks at maintenance), and 9.0 mg (6 weeks at maintenance) [7, 12].

Efficacy (body weight change from baseline at week 16):

- 2.4 mg maintenance: -4.8%

- 4.8 mg maintenance: -8.6%
- 9.0 mg maintenance: -8.3%
- Placebo: -1.7% [6, 7, 12]

Safety and tolerability:

- No serious or severe adverse events [7, 12]
- One participant discontinued after the third dose due to moderate nausea and vomiting; no other discontinuations due to adverse events [7, 12]
- Nausea: reported in 16.7 to 33.3% of active groups versus 16.7% of placebo [7, 12]
- Vomiting: two moderate events in one participant only [7, 12]
- Diarrhea: two mild events across all active groups [7, 12]
- Injection site reactions: all mild; 63% of reactions occurred in two participants [7, 12]
- No antidrug antibodies detected [7, 12]
- Mean pulse rate decreased approximately 5 beats per minute; trend toward decreased blood pressure [7]
- No clinically significant ECG, physical examination, or laboratory findings [7, 12]

Topline results were presented at Obesity Week in San Antonio, Texas on November 3 to 6, 2024 [7, 12].

7.3 Phase 2 ZUPREME-1 (NCT06662539)

A randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter, dose-finding Phase 2 trial enrolled 493 participants (53% female, mean baseline BMI 37 kg/m²) with overweight or obesity across 33 sites in the United States, Poland, and Romania [13]. Five petrelintide dose arms were evaluated against placebo, with once-weekly subcutaneous administration, dose escalation every fourth week over up to 16 weeks, and maintenance dosing until week 42, followed by a 9-week safety follow-up to week 51 [13].

Primary endpoint: Percentage change in body weight from baseline to week 28. The trial met its primary endpoint, with all five petrelintide dose arms showing statistically significant body weight reductions versus placebo at week 28 [13].

Key secondary endpoint (week 42, efficacy estimand):

- Maximally effective dose: -10.7% mean body weight reduction
- Placebo: -1.7%
- p less than 0.001 [13]

Dose escalation success: 98% of participants in the maximally effective treatment arm successfully escalated to the targeted maintenance dose [13].

Secondary endpoints: Changes in waist circumference, hemoglobin A1c, high-sensitivity C-reactive protein, fasting lipids, and fasting glucose were listed as secondary endpoints; specific numeric values for these parameters were not disclosed in the topline announcement [13]. Body composition by MRI at week 42 was an exploratory endpoint with results pending [13].

Safety and tolerability:

- Described as "placebo-like tolerability" [13]
- Vomiting at maximally effective dose: zero cases reported [13]
- Vomiting across all petrelintide arms: lower incidence than placebo [13]
- Diarrhea and constipation: single-digit percentages, consistent with placebo [13]
- Nausea: less common than in the Phase 1b trial; vast majority mild; almost no events after participants reached targeted maintenance dose [13]
- Injection site reactions: very low incidence, consistent with placebo [13]
- No safety signals for alopecia, fatigue, or neuropsychiatric adverse events (headache, depression) [13]
- Discontinuation due to adverse events: 4.8% (petrelintide, maximally effective arm) versus 4.9% (placebo) [13]
- Trial withdrawal for any reason: 8.4% (petrelintide across all arms) versus 13.6% (placebo) [13]

Sex-based differences: Female participants lost considerably more weight than male participants; specific numeric breakdown has not been disclosed [13].

Topline results were announced March 5, 2026. Full results, including the 9-week post-treatment follow-up period, are expected at a scientific conference later in 2026 [13].

7.4 Ongoing and planned trials

ZUPREME-2 (Phase 2): Petrelintide monotherapy in adults with overweight or obesity and type 2 diabetes. Topline results expected in the second half of 2026 [13].

Petrelintide plus CT-388 combination (Phase 2): A combination trial of petrelintide with CT-388 (Roche's dual GLP-1/GIP receptor agonist) was initiated in the first half of 2026 [13, 14].

Phase 3 monotherapy: Initiation planned for the second half of 2026 for chronic weight management [13, 14].

Additional pharmacokinetic studies: NCT07076030 (renal impairment) and NCT07338214 (different drug product concentrations) are registered [16, 17].

8. Sourcing and Quality Verification

Petrelintide is an investigational compound not approved for sale or clinical use in any jurisdiction. The compound is available exclusively through the sponsor (Zealand Pharma A/S) for authorized clinical trials and through select research-grade peptide suppliers for non-clinical research applications.

Research-grade petrelintide (ZP8396) is listed by MedChemExpress (catalog HY-P10745) as the acetate salt with reported purity greater than 98% by HPLC [18]. The compound is classified as a dual amylin/calcitonin receptor agonist research tool compound. CAS registry number 2766385-23-1 provides unambiguous chemical identification for procurement [3].

Investigators acquiring research-grade petrelintide should confirm identity and purity through:

- Liquid chromatography-mass spectrometry (LC-MS) confirmation of molecular weight (expected approximately 4191.7 Da for the free peptide) [5]
- Reversed-phase HPLC with UV detection for area-percent purity assessment
- Peptide content determination (accounting for acetate, water, and TFA counterion content)
- Amino acid analysis to confirm composition consistent with the 36-amino-acid sequence
- Dynamic light scattering to confirm monomeric state (expected Z-average 1.8 to 4.0 nm) and absence of fibrillation [1]

Given the structural complexity of petrelintide (lactam bridge, N-methylations, lipitation, non-standard amino acids including hydroxyproline and adipic acid), investigators should not assume that standard peptide synthesis vendors can produce material identical to the clinical-grade compound without explicit sequence and modification verification. The C20 diacid lipitation and gamma-glutamic acid linker are critical for pharmacokinetic properties; peptide lacking this moiety would have fundamentally different in vivo behavior.

9. Reconstitution and Handling

Petrelintide is a peptide formulated in aqueous solution at approximately neutral pH (6.1 to 7.4) [1]. The clinical formulation is presented as a pre-filled subcutaneous injection device (specific device format not disclosed in published literature as of monograph date).

For research-grade lyophilized material:

Reconstitution: The peptide is soluble in aqueous buffers at neutral pH. Acceptable reconstitution solvents include phosphate-buffered saline (pH 7.4), histidine buffer (pH 6.1 to 7.4), or Tris buffer (pH 6.6 to 7.4) [1]. Dimethyl sulfoxide (DMSO) may be used for concentrated stock solutions for in vitro work. Solubility exceeds 200 micromolar in aqueous buffers at pH 7.0 to 7.5 for most tested formulations [1].

Storage: Lyophilized peptide should be stored at minus 20 degrees Celsius or below. Reconstituted solutions demonstrate acceptable stability at 2 to 8 degrees Celsius; accelerated stability data show less than 3% degradation at 40 degrees Celsius over 1 month at neutral pH [1]. These data suggest robust stability under standard refrigerated research storage conditions.

Fibrillation: No fibrillation detected under any tested neutral-pH condition, including accelerated stability [1]. This eliminates the fibrillation concern that requires pramlintide to be formulated at pH 4.0 and restricts its coformulation with other peptides.

Aliquoting: Single-use aliquots are recommended to avoid repeated freeze-thaw cycles. The absence of fibrillation and low oligomerization tendency under stress conditions suggest reasonable freeze-thaw tolerance, though formal freeze-thaw cycling data for the research-grade material have not been published.

Light and oxygen sensitivity: Specific photostability and oxidative sensitivity data have not been reported in the published literature; standard peptide handling precautions (amber vials, nitrogen overlay for lyophilized stocks) are appropriate.

10. Stack Interaction Considerations

10.1 Metabolic interactions

Petrelintide is a peptide (molecular weight approximately 4192 Da) and is not expected to be metabolized by cytochrome P450 enzymes or to inhibit or induce CYP isoforms. Peptide drugs are generally cleared through proteolytic degradation and renal filtration, not through hepatic CYP-mediated biotransformation [6]. Formal drug-drug interaction studies have not been published.

The albumin-binding mechanism (reversible association with serum albumin via the C20 diacid moiety) raises theoretical potential for displacement interactions with other highly albumin-bound drugs (warfarin, phenytoin, valproic acid), though at clinical petrelintide concentrations the fraction of total albumin binding sites occupied would be negligible. No displacement interactions have been identified in clinical development.

10.2 Pharmacodynamic interactions

GLP-1 receptor agonists: The combination of amylin receptor agonism with GLP-1 receptor agonism is the principal pharmacodynamic combination of interest. Preclinical and clinical evidence with CagriSema (cagrilintide plus semaglutide) demonstrates additive or supra-additive weight loss from the combination relative to either monotherapy [19]. The Roche collaboration specifically targets a fixed-dose combination of petrelintide with CT-388 (dual GLP-1/GIP agonist) [14]. Coformulation compatibility has been demonstrated at the pharmaceutical level [1]. The combination is expected to produce greater gastrointestinal adverse events than petrelintide monotherapy, given the established GI tolerability profile of incretin-class agents.

Insulin: Pramlintide is approved as an adjunct to mealtime insulin in type 1 and type 2 diabetes [8]. Combination of petrelintide with insulin has not been studied but could produce additive hypoglycemia risk through the glucagon-suppressive mechanism of amylin receptor activation. Investigators studying this combination should implement glucose monitoring.

Gastric emptying modifiers: Petrelintide delays gastric emptying [6, 9]. Concurrent administration with other agents that slow gastric emptying (opioids, anticholinergics) could produce additive delay with clinical consequences for oral drug absorption timing. Concurrent use with prokinetic agents (metoclopramide, erythromycin) would produce pharmacodynamic opposition.

Oral medications with narrow therapeutic windows: The gastric emptying delay produced by amylin receptor activation may alter the rate (though not necessarily extent) of absorption of concurrently administered oral medications. This is a class effect shared with pramlintide and GLP-1 receptor agonists. Investigators should be alert to timing-sensitive oral medications (antibiotics, oral contraceptives, narrow-therapeutic-index drugs) administered concurrently.

10.3 Combinations of research interest

Petrelintide plus CT-388 (GLP-1/GIP dual agonist): The authorized development combination. CT-388 employs minimal beta-arrestin recruitment, enabling prolonged pharmacological activity through reduced receptor desensitization [14]. The complementary mechanisms (amylin-mediated central satiety plus incretin-mediated peripheral metabolic effects) are expected to produce best-in-disease efficacy with potentially enhanced tolerability relative to high-dose incretin monotherapy [14].

Petrelintide plus tirzepatide: Eli Lilly's combination program pairs eloralintide (their AMY1R-selective analog) with tirzepatide. Analogous research with petrelintide plus tirzepatide or similar GLP-1/GIP agonists could inform the mechanistic contribution of balanced DACRA versus selective AMY1R agonism in the combination setting [8].

11. Adverse Events and Safety Signal

11.1 Common adverse events from controlled trials

The adverse event profile of petrelintide across Phase 1 and Phase 2 trials is characterized by a gastrointestinal signal that is substantially milder than that reported for GLP-1 receptor agonist monotherapy achieving comparable weight loss [7, 12, 13]:

Phase 1b (16 weeks, n=48):

- Nausea: 16.7 to 33.3% (petrelintide) versus 16.7% (placebo) [7, 12]
- Vomiting: one participant only (moderate severity, leading to discontinuation after third dose) [7, 12]
- Diarrhea: two mild events across all active groups [7, 12]
- Decreased appetite: reported as "mild" and classified as the most common side effect [7]
- Injection site reactions: all mild; concentrated in two participants [7, 12]

Phase 2 ZUPREME-1 (42 weeks, n=493):

- Nausea: less common than in Phase 1b; vast majority mild; almost no events after reaching maintenance dose [13]
- Vomiting: zero cases at the maximally effective dose [13]
- Diarrhea and constipation: single-digit percentages, consistent with placebo [13]
- Injection site reactions: very low, consistent with placebo [13]
- No alopecia, no fatigue, no neuropsychiatric signals (headache, depression) [13]

11.2 Discontinuation rates

- Phase 1b: 1/48 (2%) discontinued due to adverse events (GI) [7, 12]
- Phase 2 ZUPREME-1: 4.8% discontinued due to AEs (petrelintide, maximally effective arm) versus 4.9% (placebo) [13]

- Trial withdrawal for any reason: 8.4% (petrelintide all arms) versus 13.6% (placebo) [13]

The lower overall withdrawal rate in the petrelintide arms compared to placebo is notable and contrasts with the typical pattern in obesity pharmacotherapy trials where active treatment arms demonstrate higher discontinuation from adverse events.

11.3 Cardiovascular observations

In the Phase 1b trial, mean pulse rate decreased approximately 5 beats per minute with petrelintide, and a trend toward decreased blood pressure was observed [7]. No clinically significant ECG findings were reported [7, 12]. Formal cardiovascular outcome data are not available at this stage of development.

11.4 Immunogenicity

No antidrug antibodies were detected in the Phase 1b trial across all dose cohorts and all participants [7, 12]. This finding is encouraging for a peptide therapeutic, though longer-duration immunogenicity data from Phase 2 and Phase 3 will be required for definitive characterization.

11.5 Context relative to GLP-1 receptor agonist tolerability

The tolerability profile of petrelintide is markedly differentiated from that of GLP-1 receptor agonists at comparable weight-loss magnitudes. For reference, in the Phase 3 STEP trial of semaglutide 2.4 mg, 44% of participants experienced nausea [8]. In the Phase 2 cagrilintide monotherapy trial, nausea rates were 24 to 31% at 2.4 mg [10]. Petrelintide's Phase 2 tolerability was described as "placebo-like" by the sponsor, with GI adverse events rates comparable to the placebo arm [13]. If confirmed in Phase 3, this tolerability advantage could translate to higher adherence and persistence rates in clinical practice, addressing a principal limitation of current obesity pharmacotherapy.

11.6 Theoretical safety considerations

Calcitonin receptor agonism and bone: Sustained calcitonin receptor activation in osteoclasts produces calcitonin escape (tachyphylaxis) in the context of calcitonin treatment for osteoporosis and Paget's disease. Whether petrelintide's balanced DACRA profile produces clinically relevant effects on bone remodeling markers has not been reported. Long-term bone density monitoring in Phase 3 would be appropriate.

Area postrema activation and nausea ceiling: The area postrema lacks a blood-brain barrier and is the emetic chemoreceptor trigger zone. Amylin analog activation of this region mediates both the therapeutic satiety effect and the nausea side effect. The favorable GI tolerability of petrelintide relative to GLP-1 agonists may reflect receptor selectivity differences, the absence of GLP-1-mediated peripheral GI effects, or dose-escalation strategy optimization. The underlying mechanism of the tolerability advantage has not been formally characterized.

12. Comparative Assessment

This section presents a structured comparative assessment of five compounds in the amylin receptor agonist and related obesity pharmacotherapy space against petrelintide, evaluated on five competency standards: novelty of mechanism, effect size for weight reduction, promising potential (current clinical trajectory), side-effect profile, and overall validation.

12.1 Cagrilintide (Novo Nordisk)

Mechanism: Long-acting acylated analog of human amylin with non-selective agonism at CTR, AMY1R, and AMY3R [10, 15]. Cagrilintide activates all calcitonin-family receptors with broadly similar potency; weight loss is mediated specifically through AMY1R and AMY3R in the brain, as demonstrated by loss of efficacy in RAMP1/3 knockout mice [15].

Development trajectory: Novo Nordisk advanced cagrilintide through a Phase 2 dose-finding trial (Lau et al. 2021) in 706 adults with overweight or obesity, demonstrating dose-dependent weight loss of 6 to 10.8% over 26 weeks (versus 3% placebo and 9% liraglutide 3.0 mg active comparator) at doses of 0.3 to 4.5 mg once weekly [10]. The compound was subsequently advanced primarily as a combination partner with semaglutide (CagriSema), which in Phase 3 achieved up to 22.7% weight loss [19]. Cagrilintide monotherapy development has been deprioritized in favor of the combination.

Effect size: Monotherapy: 6 to 10.8% at 26 weeks in Phase 2 [10]. Combination (CagriSema): up to 22.7% in Phase 3 [19].

Side-effect profile: Phase 2 monotherapy nausea rates of 24 to 31% at 2.4 mg dose [8, 10]. Higher conditioned taste aversion liability than eloralintide in preclinical models (ED50 4.2 versus 8.9 nmol/kg) [8]. In the combination, GI tolerability is dominated by the semaglutide component.

Comparison to petrelintide: Cagrilintide and petrelintide are the two most direct comparators as long-acting amylin analogs in clinical development. Cagrilintide is further advanced (Phase 3 in combination). Petrelintide's balanced DACRA profile (equipotent at AMY3R and CTR) differs from cagrilintide's non-selective profile.

Petrelintide's Phase 2 tolerability (placebo-like, zero vomiting) appears substantially superior to cagrilintide monotherapy (24 to 31% nausea). Petrelintide's Phase 2 weight loss (10.7% at 42 weeks) is broadly comparable to cagrilintide (10.8% at 26 weeks at the highest dose, though trial design differences preclude direct comparison). The coformulation compatibility of petrelintide at neutral pH may offer manufacturing advantages for fixed-dose combinations.

Scores (1 to 5): Novelty: 3. Effect size: 4. Promising potential: 4. Side-effect profile: 3. Overall validation: 4.

12.2 Eloralintide (LY3841136, Eli Lilly)

Mechanism: AMY1R-selective long-acting amylin analog. Approximately 12-fold more potent at human AMY1R than CTR, and 11-fold more potent at AMY1R than AMY3R [8]. Structural modifications include a methylene thioacetal bridge (replacing the native disulfide), three non-coded amino acids at positions 11, 15, and 22, and C20 fatty diacid at Lys26 for albumin binding [8].

Development trajectory: Eli Lilly completed a Phase 1 SAD study (48 participants, BMI 27.5 kg/m²) demonstrating dose-dependent weight loss: -2.5% at 4 mg (p less than 0.01 versus placebo) and -4.4% at 12 mg (p less than 0.001 versus placebo) at day 29 [8]. Multiple Phase 2 and Phase 3 trials are ongoing both as monotherapy and in combination with tirzepatide (NCT06230523, NCT06297616, NCT06915091, NCT06603571) [8].

Effect size: Phase 1 single-dose: -4.4% at day 29 at 12 mg [8]. Multiple-dose efficacy data are pending from ongoing Phase 2/3 trials.

Side-effect profile: Notably favorable in Phase 1: only 2 of 36 active-treatment participants reported GI events (one vomiting at 12 mg, one dyspepsia). No serious adverse events, no discontinuations [8]. Preclinically, eloralintide induced significantly less conditioned taste aversion than cagrilintide [8].

Comparison to petrelintide: Eloralintide and petrelintide differ in receptor selectivity (AMY1R-selective versus balanced DACRA). Eloralintide's half-life is longer (310 to 366 hours, approximately 13 to 15 days, versus approximately 240 hours for petrelintide) [8]. Both demonstrate substantially better GI tolerability than cagrilintide. Eloralintide is slightly earlier in clinical development (Phase 1 data only pub-

lished in detail), but Eli Lilly's Phase 2/3 program with the tirzepatide combination has advanced aggressively. The clinical relevance of AMY1R selectivity versus balanced DACRA activity remains an open scientific question.

Scores (1 to 5): Novelty: 3. Effect size: 3 (limited Phase 1 data). Promising potential: 4. Side-effect profile: 5. Overall validation: 3.

12.3 Pramlintide (Symlin, approved 2005)

Mechanism: Synthetic analog of human amylin with Pro25, Pro28, and Pro29 substitutions to reduce fibrillation tendency, but retaining the native disulfide bridge [8, 20]. Non-selective amylin receptor agonist. Approved by the FDA as an adjunct to mealtime insulin in type 1 and type 2 diabetes for glycemic control with modest secondary weight benefit [20].

Development trajectory: Developed by Amylin Pharmaceuticals, approved 2005. Requires three-times-daily subcutaneous injection prior to meals due to short circulating half-life. Formulated at acidic pH (4.0) because of residual fibrillation at neutral pH, preventing coformulation with insulin [8, 20]. Development for obesity as a standalone indication was explored in combination with phentermine and metreleptin but did not advance to registration [20].

Effect size: Glycemic: 0.4 to 0.6% HbA1c reduction as insulin adjunct [6, 20]. Weight: approximately 1 to 2 kg weight loss over 6 to 12 months in diabetes trials, insufficient for standalone obesity registration [20].

Side-effect profile: Nausea is the principal adverse event (approximately 30 to 50% in early trials, improving with dose titration). Hypoglycemia risk when combined with insulin (mitigated by insulin dose reduction) [20]. Injection site reactions common.

Comparison to petrelintide: Pramlintide is the only approved amylin analog and serves as the class reference. Petrelintide represents a generational advance: once-weekly versus three-times-daily dosing, neutral-pH stability versus acidic pH required, coformulatable with other peptides versus isolated administration, 10.7% weight loss versus 1 to 2 kg weight loss. The structural innovations (lactam bridge, N-methylations, asparagine deletions, lipidation) that enabled petrelintide's pharmacokinetic and stability profile are the principal medicinal chemistry advances over pramlintide.

Scores (1 to 5): Novelty: 2. Effect size: 1. Promising potential: 1. Side-effect profile: 2. Overall validation: 4 (established by approval, but limited efficacy).

12.4 Amycretin (Novo Nordisk)

Mechanism: First-in-class unimolecular dual GLP-1 and amylin receptor agonist, combining both agonist activities in a single peptide molecule [21]. Available as both subcutaneous (once-weekly) and oral (once-daily) formulations [21].

Development trajectory: Phase 1b/2a results (Dahl et al. 2025, Lancet) in 125 randomized participants demonstrated extraordinary dose-dependent weight loss: -9.7% at 1.25 mg (20 weeks), -16.2% at 5 mg (28 weeks), -22.0% at 20 mg (36 weeks), and -24.3% at 60 mg (36 weeks), versus -1.1% to +2.3% placebo [21]. The oral formulation achieved 13% weight loss at 16 weeks in a separate Phase 1 trial [21]. Multiple Phase 2 trials are ongoing.

Effect size: -24.3% at 36 weeks at highest dose (subcutaneous) [21]. This represents the highest reported weight loss for any obesity pharmacotherapy in early-phase development, attributed to the dual mechanism combining incretin and amylin receptor activation in a single molecule.

Side-effect profile: Gastrointestinal events were most common, consistent with expectations for GLP-1 and amylin agonists, with the majority mild to moderate and resolving by study end [21]. A high proportion of participants withdrew for reasons unrelated to adverse events. The GI event rate appears similar to early-phase GLP-1 agonist studies [21].

Comparison to petrelintide: Amycretin and petrelintide represent different strategic approaches. Petrelintide is a pure amylin-class agent designed for combination with a separate incretin molecule; amycretin integrates both mechanisms in one molecule. Amycretin achieves substantially greater weight loss (24.3% versus 10.7%), but this comparison is confounded by the dual mechanism (the GLP-1 component independently produces weight loss). Petrelintide's dramatically superior GI tolerability (placebo-like versus typical GLP-1 profile) is the principal differentiator and may translate to better adherence in the population intolerant of incretin-class side effects. The petrelintide plus CT-388 combination is designed to match or exceed amycretin's efficacy while potentially offering modularity in dose adjustment.

Scores (1 to 5): Novelty: 5. Effect size: 5. Promising potential: 5. Side-effect profile: 3. Overall validation: 3 (early-phase only).

12.5 CagriSema (cagrilintide 2.4 mg + semaglutide 2.4 mg, Novo Nordisk)

Mechanism: Fixed-dose combination of a long-acting amylin analog (cagrilintide) with a GLP-1 receptor agonist (semaglutide 2.4 mg), both administered once weekly in separate injections [19]. The combination targets complementary central and peripheral satiety, metabolic, and gastric emptying mechanisms. This represents the combination strategy that petrelintide plus CT-388 is designed to compete with.

Development trajectory: CagriSema completed Phase 3 in adults with overweight or obesity, achieving up to 22.7% weight loss [19]. A Phase 3 trial in type 2 diabetes (reported in NEJM 2025) demonstrated superiority over semaglutide monotherapy [19]. Regulatory submission is anticipated.

Effect size: Up to 22.7% weight loss in Phase 3 (superior to either monotherapy) [19].

Side-effect profile: The GI tolerability profile is dominated by the semaglutide component, with nausea, vomiting, and diarrhea rates consistent with GLP-1 receptor agonist class labeling. The addition of cagrilintide does not appear to substantially worsen GI tolerability beyond what semaglutide alone produces [19].

Comparison to petrelintide: CagriSema is the nearest strategic competitor to the petrelintide plus CT-388 combination. Both are amylin-plus-incretin strategies in separate-molecule combinations. Petrelintide's tolerability advantage (if maintained in combination) and neutral-pH coformulation capability (enabling a single fixed-dose injection rather than two separate injections) are the principal potential differentiators. CagriSema is substantially further advanced (Phase 3 complete versus Phase 2 for petrelintide monotherapy and Phase 2 planned for combination).

Scores (1 to 5): Novelty: 3. Effect size: 5. Promising potential: 5. Side-effect profile: 3. Overall validation: 5.

12.6 Comparator summary

The five comparators span the amylin and combination obesity pharmacotherapy landscape. **Cagrilintide** is the most direct monotherapy comparator with broadly similar weight loss but inferior GI tolerability. **Eloralintide** represents an AMY1R-selective alternative with exceptional early tolerability data but limited published efficacy. **Pramlintide** is the class reference, superseded by the long-acting analogs in all performance metrics except regulatory approval status. **Amycretin** achieves the highest reported weight loss through dual GLP-1/amylin agonism but at the cost of typical GLP-1 GI tolerability. **CagriSema** demonstrates the clinical potential of amylin-plus-incretin combinations and is the benchmark the petrelintide plus CT-388 program must meet or exceed.

Petrelintide's distinctive positioning within this landscape rests on three claims: (1) placebo-like GI tolerability at clinically meaningful weight loss, which if confirmed in Phase 3 could address the principal adherence barrier in obesity pharmacotherapy; (2) neutral-pH chemical stability enabling coformulation in fixed-dose combinations with incretin-class partners; (3) balanced DACRA pharmacology (equipotent AMY3R and CTR agonism) that may access mechanisms distinct from AMY1R-selective or non-selective agents. The clinical relevance of claim (3) remains to be established. Claims (1) and (2) are supported by Phase 2 data and pharmaceutical characterization data, respectively.

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