

RESEARCH MONOGRAPH . COMPOUND PROFILE

Dapiglutide

A first-in-class 33-amino-acid acylated peptide dual agonist of the glucagon-like peptide 1 and glucagon-like peptide 2 receptors developed by Zealand Pharma for the treatment of obesity and obesity-associated low-grade inflammation, distinguished from conventional incretin-class therapeutics by the addition of GLP-2-receptor-mediated intestinal barrier repair and anti-inflammatory activity to GLP-1-receptor-mediated anorectic and glucometabolic effects.

DOCUMENT	KDC-MN-1413
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi <i>ac</i> biolabs Research
COMPOUND CLASS	Dual GLP-1/GLP-2 receptor agonist peptide with biased signaling and prolonged pharmacokinetics

RESEARCH USE ONLY

ABSTRACT

Dapiglutide (ZP 7570; CAS 2296814-85-0; molecular formula C₁₉₂H₃₀₂N₄₆O₅₇; molecular weight 4166.79 g/mol) is a synthetic 33-amino-acid peptide dual agonist of the human glucagon-like peptide 1 receptor (GLP-1R) and glucagon-like peptide 2 receptor (GLP-2R) bearing a C18 fatty acid acyl modification that extends plasma half-life to approximately 123 to 129 hours and permits once-weekly subcutaneous administration [1, 2]. Developed by Zealand Pharma A/S (Copenhagen, Denmark) as a potential first-in-class agent for obesity and its inflammatory comorbidities, dapiglutide was designed to exploit the complementary pharmacology of the two incretin receptors: GLP-1R activation suppresses appetite, delays gastric emptying, and improves glucose homeostasis through cyclic adenosine monophosphate (cAMP)-dependent signaling in pancreatic beta cells, hypothalamic appetite circuits, and vagal afferents; GLP-2R activation promotes intestinal epithelial proliferation, enhances paracellular tight junction integrity, and suppresses mucosal inflammation through cAMP-dependent signaling in enteroendocrine cells, subepithelial myofibroblasts, and enteric neurons [3, 4]. At the molecular level, dapiglutide exhibits biased agonism at the GLP-1R, displaying full agonist activity for cAMP formation while producing significantly blunted beta-arrestin recruitment, a signaling profile associated with reduced receptor desensitization and sustained intracellular cAMP production for up to 12 hours in vitro [5]. The compound entered clinical development in 2020 with a Phase 1 single-ascending-dose and multiple-ascending-dose trial in healthy volunteers demonstrating dose-proportional pharmacokinetics, a favorable

safety profile dominated by mild gastrointestinal adverse events, and dose-dependent body weight reductions of up to 4.3 percent from baseline after four weeks of once-weekly dosing [1, 2]. A subsequent 13-week Phase 1b multiple-ascending-dose extension in 54 participants with overweight or obesity (BMI 27 to 40 kg/m²) reported placebo-adjusted body weight reductions of up to 8.3 percent, with no severe treatment-emergent adverse events [6]. A 28-week extension of the same trial (Part 2, 30 participants, doses up to 26 mg weekly) reported mean body weight reduction of 11.6 percent versus 0.2 percent on placebo, with continued favorable tolerability [7]. An investigator-led mechanistic trial (DREAM; 54 participants with obesity, BMI greater than or equal to 30 kg/m²) evaluated lower doses (4 mg and 6 mg) over 12 weeks and reported body weight reductions of 2.9 and 4.3 percent respectively versus 2.2 percent on placebo; the primary endpoint did not achieve statistical significance, though HbA1c reduction was significant at 6 mg [8, 9]. The preclinical pharmacology of dapiglutide includes demonstration of intestinal barrier repair in murine short bowel syndrome models, where the compound promoted claudin-7 expression, tightened the paracellular leak pathway, improved oral glucose tolerance, reduced intestinal transit time, increased villus height and intestinal length, and reduced stool water losses [10, 11]. Zealand Pharma paused the dapiglutide program in 2025, citing portfolio prioritization in an increasingly competitive metabolic disease landscape, though the Phase 1b 28-week data were subsequently reported as positive [7, 12]. The compound is not approved in any jurisdiction. It is available from select research chemical suppliers for investigational use only.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: Dapiglutide.

Development codes: ZP 7570, ZP-7570 (Zealand Pharma). The development code is the canonical identifier in the early pharmacology literature and in the ClinicalTrials.gov registrations.

Chemical Abstracts Service registry number: 2296814-85-0.

PubChem Compound Identifier: 171934788.

DrugBank identifier: DB19182.

Unique Ingredient Identifier (UNII): J43GMI6IYW.

International Union of Pure and Applied Chemistry name: Not formally assigned for macromolecular peptides of this size; the compound is defined by its amino acid sequence and lipid modification rather than by a single systematic organic name.

1.2 Structural class and chemistry

Dapiglutide is a synthetic linear peptide of 33 amino acid residues bearing a C18 (stearic acid) fatty acyl chain conjugated to the peptide backbone through a linker moiety [1]. The acylation strategy is analogous to the albumin-binding fatty acid modifications employed in semaglutide (C18 fatty diacid) and liraglutide (C16 palmitoyl chain) to extend plasma half-life through reversible non-covalent albumin binding in circulation. The structural class places dapiglutide within the incretin mimetic peptide family, specifically the GLP-1/GLP-2 hybrid agonist subclass.

Molecular formula: C₁₉₂H₃₀₂N₄₆O₅₇ [13].

Molecular weight: 4166.79 g/mol (monoisotopic mass of the complete acylated peptide) [13].

Physical properties: The compound is expected to present as a white to off-white lyophilized powder. Soluble in aqueous buffer at physiological pH; solubility in dimethyl sulfoxide is expected for stock solution preparation at research concentrations. Stability data for the lyophilized form have not been published; by analogy with structurally related acylated GLP-1 peptides, storage at minus 20 degrees Celsius in desiccated conditions is expected to preserve integrity for at least 12 months.

Stereochemistry: All amino acid residues are in the L-configuration as is standard for bioactive peptide therapeutics. The fatty acyl chain introduces no additional stereocenters.

1.3 Synthesis

The detailed synthetic route for dapiglutide has not been disclosed in the peer-reviewed literature. By analogy with other acylated incretin peptides of similar length and modification pattern, the synthesis is expected to proceed through solid-phase peptide synthesis (Fmoc strategy) on a resin support, with sequential deprotection-coupling cycles for the 33 amino acid residues, followed by on-resin or solution-phase conjugation of the C18 fatty acid through an appropriate linker (glutamic acid spacer or similar), global deprotection, resin cleavage, and purification by preparative reversed-phase high-performance liquid chromatography [14]. The acylation step is the critical modification that converts a short-acting peptide into a long-acting albumin-binding formulation suitable for once-weekly dosing. Industrial-scale production of acylated peptides of this class has been demonstrated for semaglutide and liraglutide at kilogram scale.

2. Abstract

Dapiglutide (ZP 7570) is a potential first-in-class long-acting dual agonist of the glucagon-like peptide 1 receptor (GLP-1R) and the glucagon-like peptide 2 receptor (GLP-2R), developed by Zealand Pharma A/S for the treatment of obesity and obesity-associated inflammatory comorbidities [1, 2]. The compound is a synthetic 33-amino-acid peptide modified with a C18 fatty acyl chain that enables reversible albumin binding, extending the plasma elimination half-life to approximately 123 to 129 hours and supporting once-weekly subcutaneous administration [2].

The dual-receptor mechanism distinguishes dapiglutide from approved GLP-1R monoagonists (semaglutide, liraglutide, dulaglutide, exenatide) and from dual GLP-1R/GIP receptor agonists (tirzepatide) by adding GLP-2R-mediated intestinal trophic, barrier-repair, and anti-inflammatory activity to the established GLP-1R-mediated appetite suppression and glucometabolic improvement [3, 4]. At the molecular pharmacology level, dapiglutide displays biased agonism at the GLP-1R with full cAMP formation efficacy but significantly reduced beta-arrestin recruitment, a profile that correlates with reduced receptor internalization and sustained intracellular signaling [5].

Clinical development has produced Phase 1b data demonstrating dose-dependent weight loss of up to 11.6 percent from baseline at 28 weeks (placebo-adjusted), a pharmacokinetic profile consistent with once-weekly dosing, and a safety and tolerability profile dominated by mild-to-moderate gastrointestinal adverse events consistent with the incretin class [6, 7]. A proof-of-concept Phase 2a mechanistic trial at lower doses did not achieve the primary weight loss endpoint but demonstrated significant HbA1c reduction and favorable tolerability [8, 9]. Preclinical models in murine short bowel syndrome demonstrated that dapiglutide promotes intestinal barrier function, increases villus height and intestinal length, improves oral glucose tolerance, and reduces stool water losses [10, 11].

Zealand Pharma paused the dapiglutide program in 2025 as part of portfolio management prioritization in the increasingly competitive incretin therapeutics landscape [12]. The compound is not approved by any regulatory authority. It is available as a research-grade preparation from select suppliers for investigational purposes only.

3. Discovery and Development History

3.1 Origin and rationale

Dapiglutide was developed by Zealand Pharma A/S, a Copenhagen-based biotechnology company specializing in peptide therapeutics, as part of a program to create dual-receptor agonists that could address the metabolic and inflammatory dimensions of obesity simultaneously [1]. The scientific rationale rested on two established bodies of evidence: first, the clinical success of GLP-1R agonists (liraglutide, semaglutide) in producing substantial weight loss through appetite suppression and delayed gastric emptying; second, the preclinical and clinical evidence that GLP-2R activation promotes intestinal mucosal healing, enhances tight junction integrity, and reduces systemic inflammation through the gut-liver axis [3, 4, 15]. Zealand Pharma hypothesized that a single molecule activating both receptors could produce weight loss comparable to GLP-1R monoagonists while additionally addressing the low-grade systemic inflammation and compromised intestinal barrier function ("leaky gut") that characterize obesity and metabolic syndrome.

3.2 Preclinical development

The preclinical characterization of dapiglutide included in vitro receptor pharmacology studies demonstrating dual agonism at human GLP-1R and GLP-2R, biased signaling characterization showing cAMP-preferring pharmacology at the GLP-1R, and in vivo efficacy studies in murine models of short bowel syndrome and diet-induced obesity [5, 10, 11]. The Reiner et al. (2022) study in the *Journal of Parenteral and Enteral Nutrition* demonstrated that in mice subjected to 40 percent small bowel resection, dapiglutide promoted body weight recovery, improved oral glucose tolerance, reduced intestinal transit time, increased villus height and intestinal length, and reduced fecal water losses with corresponding reductions in plasma aldosterone [10]. A subsequent Reiner et al. (2022) study in the *Annals of the New York Academy of Sciences* extended the intestinal characterization to tight junction physiology, demonstrating that dapiglutide increased claudin-7 expression, tightened the paracellular leak pathway in the jejunum, and enhanced cation-selective tight junction function through claudin-2, claudin-10b, and claudin-15 modulation [11].

3.3 Phase 1 clinical development

Zealand Pharma initiated a first-in-human Phase 1 clinical trial of dapiglutide in 2020. The single-ascending-dose and multiple-ascending-dose study was conducted in healthy volunteers and demonstrated dose-proportional pharmacokinetics with a mean plasma half-life of 123 to 129 hours across dose cohorts, low inter-subject variability, no serious or severe adverse events, no anti-drug antibody formation, and dose-dependent body weight loss of up to 4.3 percent from baseline after four weeks of once-weekly subcutaneous dosing [1, 2]. These data were presented at the 82nd Annual American Diabetes Association Scientific Sessions in June 2022 and formed the basis for advancement to extended Phase 1b and Phase 2 development [2].

3.4 Phase 1b extension

A 13-week Phase 1b multiple-ascending-dose trial (Part 1) enrolled 54 participants (approximately 85 percent male, median age 46 years, median BMI 30.0 kg/m²) randomized 14:4 to dapiglutide or placebo within three dose cohorts escalating to 13 mg with rapid up-titration every two weeks [6]. The trial reported placebo-adjusted body weight reductions of up to 8.3 percent (mean 6.2 percent on dapiglutide versus 2.1 percent weight gain on placebo), delayed gastric emptying, and dose-dependent reductions in plasma glucose and insulin [6]. No severe treatment-emergent adverse events were observed; one serious adverse event was deemed unrelated to treatment; anti-drug antibodies were detected in 14.3 percent of dapiglutide-treated participants [6].

Part 2 of the Phase 1b trial enrolled 30 participants (approximately 93 percent male, median age 44.5 years, median baseline BMI 28.8 kg/m²) receiving 28 once-weekly doses escalated to 26 mg with up-titration every fourth week [7]. At week 28, mean body weight decreased by 11.6 percent from baseline on dapiglutide versus 0.2 percent on placebo, with no severe or serious treatment-emergent adverse events and continued favorable gastrointestinal tolerability [7].

3.5 Phase 2a proof-of-concept (DREAM trial)

The DREAM trial was a mechanistic investigator-led, randomized, placebo-controlled, parallel-group, single-center clinical trial in 54 participants with obesity (BMI greater than or equal to 30 kg/m²; median 34.8 kg/m²) [8, 9]. Participants re-

ceived once-weekly subcutaneous dapiglutide at 4 mg (titrated from 2 mg) or 6 mg (titrated from 2 mg through 4 mg) or placebo over 12 weeks. The primary endpoint of percentage change in body weight from baseline did not achieve statistical significance: 4 mg group 2.9 percent ($p = 0.483$), 6 mg group 4.3 percent ($p = 0.077$), placebo 2.2 percent [9]. However, the 6 mg group demonstrated a statistically significant reduction in HbA1c of 2.4 mmol/mol versus 0.1 mmol/mol in placebo ($p = 0.006$) [9]. No participants discontinued due to drug-related adverse effects; gastrointestinal adverse events were reported at rates lower than those observed with other incretin therapies [8, 9].

3.6 Program pause

In 2025, Zealand Pharma announced that the dapiglutide program would be paused as part of active portfolio management, with the company citing the increasingly crowded metabolic disease landscape and prioritizing investments in programs with the greatest potential for clinical differentiation [12]. The 28-week Phase 1b data (Part 2) were subsequently reported as positive, demonstrating that higher doses and longer treatment duration produced weight loss approaching that of established GLP-1R monoagonists [7]. The program remains paused as of the most recent monograph revision; the compound is not in active commercial development and no Phase 2b trial has been initiated despite earlier announcements of intent to begin in the first half of 2025.

4. Mechanism of Action

Dapiglutide is a dual-receptor agonist whose pharmacological activity is mediated through two class B1 G-protein-coupled receptors of the secretin receptor family: the glucagon-like peptide 1 receptor (GLP-1R) and the glucagon-like peptide 2 receptor (GLP-2R). These two receptors are activated by the endogenous proglucagon-derived peptides GLP-1(7-36)amide and GLP-2(1-33) respectively, both secreted from enteroendocrine L-cells of the distal small intestine and colon in response to nutrient ingestion [3, 15].

4.1 GLP-1 receptor agonism

The GLP-1 receptor is expressed at high density on pancreatic beta cells, hypothalamic appetite-regulating neurons (arcuate nucleus, paraventricular nucleus), vagal afferent neurons, gastric parietal cells, and at lower density in cardiac, renal, and hepatic tissue. Activation of the GLP-1R by dapiglutide initiates the canonical Gs-protein-coupled signaling cascade: stimulation of adenylyl cyclase, elevation of intracellular cAMP, activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC), and downstream phosphorylation of transcription factors including cAMP response element-binding protein (CREB) [3, 16].

The principal therapeutic consequences of GLP-1R activation are:

Appetite suppression: Activation of GLP-1R on hypothalamic POMC/CART neurons and inhibition of NPY/AgRP neurons in the arcuate nucleus reduces food intake. Vagal afferent GLP-1R activation signals satiety to the nucleus tractus solitarius.

Delayed gastric emptying: GLP-1R activation on gastric smooth muscle and enteric neurons slows gastric motility, contributing to postprandial satiety and reduced caloric absorption rate.

Glucose-dependent insulintropic effect: GLP-1R activation on pancreatic beta cells potentiates glucose-stimulated insulin secretion through cAMP/PKA-mediated enhancement of exocytotic machinery.

Glucagon suppression: GLP-1R signaling reduces alpha-cell glucagon secretion through paracrine and central mechanisms, contributing to postprandial glucose control.

4.2 Biased agonism at the GLP-1R

Dapiglutide displays a pharmacologically important biased signaling profile at the GLP-1R [5]. In characterization studies presented at the 2024 American Diabetes Association Scientific Sessions, dapiglutide demonstrated full agonist activity for cAMP formation (the canonical Gs-coupled pathway) while producing significantly blunted beta-arrestin-2 recruitment compared to native GLP-1 [5]. The cAMP-biased profile has several mechanistic implications:

Reduced receptor desensitization: Beta-arrestin recruitment is the principal mediator of GLP-1R phosphorylation, internalization, and desensitization. Reduced beta-arrestin engagement predicts sustained cell-surface receptor availability and prolonged cAMP signaling duration.

Sustained intracellular signaling: Dapiglutide-induced cAMP formation kinetics persisted for up to 12 hours in vitro, substantially longer than native GLP-1, potentially reflecting the combination of biased signaling, reduced receptor internalization, and the intrinsic binding properties of the modified peptide [5].

Clinical relevance: The biased signaling profile may contribute to the sustained pharmacodynamic effects observed with once-weekly dosing and may partially explain the favorable gastrointestinal tolerability (lower nausea incidence) compared to some GLP-1R agonists that recruit beta-arrestin more potently.

4.3 GLP-2 receptor agonism

The GLP-2 receptor is expressed predominantly in the gastrointestinal tract: on subepithelial myofibroblasts of the lamina propria, on enteric neurons of the submucosal and myenteric plexuses, and on enteroendocrine cells [4, 15]. The GLP-2R is a class B1 G-protein-coupled receptor that signals through Gs-adenylyl cyclase-cAMP and through downstream Akt/PI3K pathways. Activation of the GLP-2R by dapiglutide produces:

Intestinal epithelial proliferation: GLP-2R activation stimulates crypt cell proliferation, increases villus height, and extends intestinal mucosal surface area. The trophic effect is mediated in part through paracrine release of growth factors (keratinocyte growth factor, insulin-like growth factor 1) from subepithelial myofibroblasts [4, 15].

Tight junction enhancement: GLP-2R signaling upregulates claudin-7, claudin-2, claudin-10b, and claudin-15 expression and promotes their localization along the crypt-villus axis, tightening the paracellular leak pathway and enhancing cation-selective barrier function [11].

Anti-inflammatory activity: GLP-2R activation suppresses mucosal and systemic inflammation through multiple pathways: inhibition of NLRP3 inflammasome activation, reduction of lipopolysaccharide translocation across the intestinal barrier, and suppression of proinflammatory cytokine release (TNF-alpha, IL-1beta, IL-6) from lamina propria immune cells [4, 17].

Reduced intestinal transit: GLP-2R activation on enteric neurons slows intestinal transit, improving nutrient absorption and reducing stool water losses [10].

4.4 Composite dual-receptor pharmacology

The dual-receptor mechanism produces a composite pharmacological profile that cannot be achieved by either monoagonist alone. The GLP-1R component drives weight loss through appetite suppression and delayed gastric emptying; the GLP-2R component addresses the intestinal barrier dysfunction and low-grade endotoxemia that contribute to the chronic inflammatory state of obesity and metabolic syndrome [3, 4]. The hypothesis underlying dapiglutide development is that repair of intestinal barrier integrity by GLP-2R activation will reduce hepatic exposure to bacterial lipopolysaccharide, lower systemic inflammatory tone, improve hepatic insulin sensitivity, and thereby enhance the metabolic benefits of GLP-1R-mediated weight loss beyond what weight loss alone can achieve [1, 8].

The composite mechanism also predicts differential effects on gastrointestinal tolerability. GLP-1R agonism delays gastric emptying and activates central nausea circuits (area postrema), producing the dose-limiting nausea that characterizes the incretin drug class. GLP-2R agonism promotes mucosal healing and reduces intestinal inflammation, which may partially offset the gastrointestinal irritation produced by GLP-1R signaling. Clinical data from the DREAM trial suggest that

dapiglutide-treated participants reported lower rates of gastrointestinal adverse events than typically observed with GLP-1R monoagonists at equivalent weight-loss doses, though this observation requires confirmation in larger comparative trials [8, 9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Dapiglutide is administered by subcutaneous injection. Absorption from the subcutaneous depot is governed by the C18 fatty acyl modification, which promotes reversible binding to albumin in the interstitial space and in circulation. The albumin binding retards elimination and produces a prolonged absorption-distribution phase characteristic of acylated peptide therapeutics [1, 2].

Time to peak plasma concentration (T_{max}) after subcutaneous administration has not been precisely reported in published literature but is expected to be in the range of 12 to 72 hours by analogy with semaglutide (T_{max} approximately 24 to 72 hours) and other C18-acylated peptides.

Dose proportionality was demonstrated across the studied dose range in the Phase 1 trial, with low inter-subject variability in pharmacokinetic parameters [2].

5.2 Distribution

Distribution data for dapiglutide have not been published in detail. By analogy with structurally related acylated GLP-1 peptides, the compound is expected to have a relatively low volume of distribution (approximately 0.05 to 0.1 L/kg) reflecting high plasma protein binding (predominantly to albumin through the C18 fatty acid chain). Plasma protein binding for semaglutide (the closest structural analog with published data) exceeds 99 percent; similar binding is expected for dapiglutide.

Central nervous system penetration sufficient for hypothalamic appetite-circuit engagement is implied by the clinical weight-loss efficacy, though the mechanism may be partially or wholly mediated by vagal afferent signaling from peripheral GLP-1R activation rather than by direct blood-brain barrier penetration of the intact peptide.

5.3 Metabolism

The metabolic fate of dapiglutide has not been characterized in published studies. By analogy with other acylated GLP-1 peptides, the compound is expected to be cleared primarily by proteolytic degradation (ubiquitous tissue peptidases) and by fatty acid beta-oxidation of the released acyl chain, rather than by cytochrome P450-mediated hepatic biotransformation. This metabolic profile predicts minimal drug-drug interaction potential through CYP-mediated pathways.

5.4 Elimination

Plasma elimination half-life: 123 to 129 hours (approximately 5.1 to 5.4 days) across four dose cohorts in the Phase 1 trial [2]. This half-life is comparable to semaglutide (approximately 168 hours) and substantially longer than liraglutide (approximately 13 hours) and native GLP-1 (approximately 2 minutes).

The half-life supports once-weekly subcutaneous dosing with minimal peak-to-trough plasma concentration fluctuation at steady state. Steady-state concentrations are predicted to be achieved after approximately 4 to 5 half-lives (3 to 4 weeks of weekly dosing), consistent with the dose escalation schemes employed in clinical trials.

5.5 Routes of administration

The only route studied in clinical trials is subcutaneous injection, administered once weekly. The injection sites used in clinical trials have not been specified in published reports but are expected to follow the standard subcutaneous injection sites for incretin peptides (abdomen, thigh, upper arm).

Oral administration is not feasible for a 4167-dalton peptide without extensive formulation modification (absorption enhancers, enteric protection). Intravenous administration has not been studied and is not relevant to the clinical application.

5.6 Special populations

No published data exist on the pharmacokinetics of dapiglutide in renal impairment, hepatic impairment, pediatric populations, or elderly populations. By analogy with semaglutide (which shows no clinically relevant pharmacokinetic changes

in mild-to-moderate renal or hepatic impairment), the proteolytic clearance mechanism predicts limited impact of organ impairment on dapiglutide disposition.

6. Preclinical Pharmacology

6.1 Murine short bowel syndrome model

The principal preclinical efficacy data for dapiglutide derive from a murine model of short bowel syndrome developed at the University of Greifswald [10]. Mice subjected to 40 percent proximal small bowel resection received dapiglutide or vehicle. Compared to vehicle-treated animals, dapiglutide-treated animals demonstrated:

- Significant improvement in oral glucose tolerance
- Reduced intestinal transit time
- Increased villus height in the remnant small bowel
- Increased total intestinal length
- Promoted body weight recovery despite unchanged liquid diet intake
- Reduced stool water losses
- Reduced plasma aldosterone (reflecting improved fluid homeostasis) [10]

These findings establish that the dual GLP-1/GLP-2 mechanism translates to functional intestinal improvement in a model of intestinal insufficiency and support the hypothesis that GLP-2R activation produces trophic effects that are preserved in the context of concurrent GLP-1R activation.

6.2 Intestinal barrier function studies

The Reiner et al. (2022) tight junction physiology study characterized dapiglutide's effects on paracellular barrier function in the murine short bowel model [11]. In the jejunum, dapiglutide:

- Increased claudin-7 expression (a barrier-tightening claudin)
- Tightened the paracellular leak pathway
- Promoted cation-selective tight junction function through extension of claudin-2 and claudin-10b expression
- Preserved claudin-15 expression and localization along the crypt-villus axis

In the colon, no significant barrier effects from dapiglutide were observed, suggesting that the GLP-2R-mediated barrier effects are region-specific to the small intestine [11]. The regional specificity is consistent with the known distribution of GLP-2R expression (highest in duodenum and jejunum, declining distally).

6.3 Diet-induced obesity models

Published preclinical data on dapiglutide in diet-induced obesity models are limited. A related study of a dual GLP-1/GLP-2 receptor agonist (GUB09-145, a structural predecessor) in diet-induced obese mice demonstrated marked weight loss, improved glucose tolerance, reduced plasma cholesterol, and favorable changes in gut microbiome composition compared to a GLP-1R monoagonist [18]. These data provide preclinical proof-of-concept for the dual-receptor approach to obesity, though the specific GUB09-145 compound differs structurally from dapiglutide.

6.4 In vitro receptor pharmacology

Dapiglutide demonstrates full agonist activity at both human GLP-1R and human GLP-2R in heterologous expression systems [5]. At the GLP-1R, the compound produces maximal cAMP responses equivalent to native GLP-1(7-36)amide while producing significantly attenuated beta-arrestin-2 recruitment (biased agonism). The cAMP formation kinetics are prolonged relative to native GLP-1, with sustained elevated cAMP detectable for up to 12 hours post-stimulation in cellular assays [5]. Specific EC50 values for cAMP formation and beta-arrestin recruitment at the GLP-1R and GLP-2R have not been disclosed in the peer-reviewed literature.

7. Clinical Evidence Base

7.1 Phase 1 single- and multiple-ascending-dose trial

The first-in-human Phase 1 trial was a single-center, randomized, double-blind, placebo-controlled study in healthy volunteers conducted in 2020 to 2021 [1, 2]. The single-ascending-dose component established safety and initial pharmacokinetic parameters. The multiple-ascending-dose component (four dose cohorts, once-weekly subcutaneous dosing for four weeks) demonstrated:

- Dose-proportional pharmacokinetics with mean half-life of 123 to 129 hours
- Low inter-subject variability
- Dose-dependent body weight loss of up to 4.3 percent from baseline after four weeks
- No serious or severe adverse events
- No anti-drug antibody formation
- Gastrointestinal adverse events (nausea, reduced appetite) consistent with GLP-1R agonist class effects [2]

7.2 Phase 1b multiple-ascending-dose extension (Part 1, 13 weeks)

The 13-week extension enrolled 54 participants with overweight or obesity (BMI 27 to 40 kg/m²; median 30.0; approximately 85 percent male; median age 46 years) randomized 14:4 (dapiglutide:placebo) within three dose cohorts with rapid up-titration every two weeks to maximum doses of 13 mg [6]. Results:

- Placebo-adjusted body weight reduction of up to 8.3 percent at week 13
- Mean weight loss on dapiglutide: 6.2 percent; mean weight gain on placebo: 2.1 percent
- Dose-dependent delayed gastric emptying
- Dose-dependent reductions in plasma glucose and insulin
- No severe treatment-emergent adverse events
- One serious adverse event deemed unrelated to treatment

- Two participants discontinued due to gastrointestinal adverse events
- Anti-drug antibodies in 14.3 percent of dapiglutide-treated participants
- Low incidence of injection site reactions (all mild) [6]

7.3 Phase 1b extension (Part 2, 28 weeks)

The 28-week extension enrolled 30 participants (approximately 93 percent male, median age 44.5 years, median baseline body weight 91.9 kg, median baseline BMI 28.8 kg/m²) receiving once-weekly doses escalated to 26 mg with up-titration every fourth week [7]. No lifestyle modifications were implemented. Results:

- Mean body weight reduction of 11.6 percent from baseline on dapiglutide versus 0.2 percent on placebo at week 28
- No severe or serious treatment-emergent adverse events
- Most adverse events mild in severity
- Gastrointestinal events (nausea, vomiting) most common
- Two participants withdrew due to adverse events
- Mild injection site reactions in a small number of participants [7]

7.4 DREAM proof-of-concept trial (Phase 2a)

The DREAM trial was a mechanistic investigator-led, randomized, double-blind, placebo-controlled, parallel-group, single-center trial conducted in Denmark in 54 participants with obesity (BMI greater than or equal to 30 kg/m²; median 34.8 kg/m²) [8, 9]. Participants received 12 weeks of once-weekly subcutaneous dapiglutide at:

- 4 mg (titrated from 2 mg after 3 weeks; n = 18)
- 6 mg (titrated from 2 mg through 4 mg after 3 and 6 weeks respectively; n = 18)
- Placebo (n = 18)

Primary endpoint: Percentage change in body weight from baseline to week 12.

Results:

- 4 mg: 2.9 percent weight loss (p = 0.483 vs placebo)
- 6 mg: 4.3 percent weight loss (p = 0.077 vs placebo)

- Placebo: 2.2 percent weight loss

The primary endpoint did not achieve statistical significance at either dose. However, the 6 mg group demonstrated a statistically significant reduction in HbA1c (2.4 mmol/mol reduction vs 0.1 mmol/mol in placebo; $p = 0.006$), suggesting preserved glucometabolic activity at these lower doses [9].

Safety: The compound was well tolerated, with no participants discontinuing due to drug-related adverse effects. Most common adverse events: reduced appetite (61 percent), nausea (56 percent), vomiting (11 percent). Gastrointestinal adverse event rates appeared lower than those reported with other incretin therapies at comparable weight-loss efficacy [8, 9].

Interpretation: The investigators concluded that the 4 mg and 6 mg doses over 12 weeks were insufficient to produce statistically significant weight loss versus placebo and that future trials would require higher doses, longer duration, or both. Detailed results on cardiovascular risk markers, systemic inflammatory markers, and gut biopsy data were announced for future scientific presentation [8].

7.5 Oral presentation at ADA 2025

Safety, tolerability, and clinical effects of dapiglutide were presented as an oral presentation (141-OR) at the 2025 American Diabetes Association Scientific Sessions, though full publication of these data in a peer-reviewed journal has not yet occurred as of the monograph revision date [19].

8. Sourcing and Quality Verification

Dapiglutide is not a marketed pharmaceutical product and is not available from conventional pharmaceutical suppliers. Research-grade dapiglutide is available from select specialty chemical suppliers including AbMole BioScience (catalog number M19693; CAS 2296814-85-0) and potentially other peptide research suppliers [20]. The compound may be listed under both its proposed INN (dapiglutide) and its development code (ZP 7570 or ZP7570).

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

- Reversed-phase high-performance liquid chromatography area-percent purity assessment (target greater than 95 percent)
- Mass spectrometry confirmation of molecular weight (expected [M+H]⁺ consistent with the 4166.79 g/mol calculated mass)
- Amino acid analysis to confirm composition
- Endotoxin testing (limulus amebocyte lysate assay) for any preparation intended for in vivo administration
- Peptide content determination (net peptide content may be 60 to 80 percent of gross weight for lyophilized peptides due to adsorbed water, counterions, and residual salts)

Given the investigational status of dapiglutide and the limited supplier base, lot-to-lot variability is possible and independent analytical confirmation of each lot is strongly recommended for any investigation where dose-response precision is important. Third-party analytical laboratories experienced with peptide characterization should be engaged where in-house capability is insufficient.

9. Reconstitution and Handling

Dapiglutide is expected to be supplied as a lyophilized powder for research applications. Reconstitution and handling recommendations are extrapolated from the general properties of acylated GLP-1 peptides of similar size and modification pattern:

Storage (lyophilized): Minus 20 degrees Celsius, desiccated, protected from light. Expected stability of at least 12 months under these conditions.

Reconstitution: Dissolve in sterile water for injection, phosphate-buffered saline (pH 7.4), or 10 percent dimethyl sulfoxide in aqueous buffer for in vitro applications. Gentle swirling rather than vortexing is recommended to avoid peptide aggregation at the air-water interface.

Stock concentration: Prepare stock solutions at 1 to 10 mg/mL. Higher concentrations may promote aggregation depending on buffer composition and pH.

Storage (reconstituted): Use immediately after reconstitution or aliquot and store at minus 20 degrees Celsius. Avoid repeated freeze-thaw cycles (maximum 3 cycles recommended). Refrigerated storage (2 to 8 degrees Celsius) of reconstituted solutions should be limited to 7 days maximum.

Compatibility: Acylated peptides may adsorb to glass and polypropylene surfaces at low concentrations. For dilute working solutions (below 0.1 mg/mL), use low-binding polypropylene tubes or glass vials pre-coated with bovine serum albumin (0.1 percent) to minimize surface losses.

Sterile filtration: The compound is expected to pass through 0.22-micrometer sterile filters without significant retention, though filter binding losses should be assessed at low concentrations.

10. Stack Interactions and Combinations

Dapiglutide's pharmacokinetic profile (proteolytic degradation, minimal CYP involvement) predicts a low potential for cytochrome P450-mediated drug-drug interactions. However, several pharmacodynamic interactions merit consideration for research applications:

Other GLP-1R agonists: Concurrent use with semaglutide, liraglutide, dulaglutide, exenatide, or tirzepatide produces pharmacological redundancy at the GLP-1R and predictable additive gastrointestinal adverse events (nausea, vomiting, diarrhea). The combination is not recommended.

GLP-2R agonists (teduglutide, glepaglutide): Concurrent use with approved or investigational GLP-2R agonists produces additive intestinal trophic effects. The combination has not been studied and the safety of supraphysiological GLP-2R stimulation with respect to intestinal neoplasia risk (a theoretical concern with chronic GLP-2R activation) is unknown.

Insulin and insulin secretagogues: GLP-1R agonism potentiates glucose-dependent insulin secretion. Concurrent use with exogenous insulin, sulfonylureas, or meglitinides increases hypoglycemia risk. Dose adjustment of the insulin or secretagogue is appropriate.

Drugs affecting gastric emptying: GLP-1R-mediated delayed gastric emptying may alter the absorption kinetics of co-administered oral drugs with narrow therapeutic windows. Agents with absorption critically dependent on gastric emptying rate (levothyroxine, oral contraceptives, warfarin, narrow-therapeutic-index antibiotics) should be monitored for altered exposure.

Anti-inflammatory agents: The GLP-2R-mediated anti-inflammatory activity of dapiglutide may produce additive effects with concurrent immunosuppressive or anti-inflammatory therapy (corticosteroids, TNF-alpha inhibitors, JAK inhibitors). The clinical significance of this interaction is unknown but is not expected to produce adverse consequences.

Antiemetics: The gastrointestinal adverse events of dapiglutide (nausea, vomiting) may be managed with concurrent 5-HT₃ receptor antagonists (ondansetron) or dopamine antagonists (metoclopramide). Metoclopramide, as a prokinetic agent, may partially counteract the GLP-1R-mediated gastric emptying delay. This pharmacological opposition should be considered in dose-response research.

Orlistat and other lipase inhibitors: Concurrent use may produce additive gastrointestinal adverse events (steatorrhea from orlistat combined with nausea from dapiglutide) without established synergistic weight-loss benefit.

11. Adverse Events and Safety Signal

11.1 Common adverse events

The adverse event profile of dapiglutide across all clinical trials is consistent with the known class effects of GLP-1R agonists, with gastrointestinal events predominating:

- Reduced appetite (up to 61 percent in the DREAM trial) [9]
- Nausea (up to 56 percent in the DREAM trial; dose-dependent across all trials) [6, 7, 9]
- Vomiting (up to 11 percent) [9]
- Injection site reactions (mild, low incidence) [6, 7]

The gastrointestinal adverse event rates in the Phase 1b extension trials were described as "consistent with clinical trials of other incretin-based therapies" [6], while the DREAM trial investigators noted that rates appeared "lower than reported with other incretin therapies" at comparable weight-loss efficacy [8, 9]. Whether the lower gastrointestinal burden reflects the GLP-2R-mediated mucosal protection, the biased GLP-1R signaling profile (reduced beta-arrestin recruitment), or simply the lower doses employed in DREAM remains to be determined.

11.2 Serious adverse events

No severe or serious treatment-emergent adverse events attributed to dapiglutide have been reported across the Phase 1 and Phase 1b clinical trials [2, 6, 7]. One serious adverse event in the 13-week Phase 1b trial was deemed unrelated to study treatment [6].

11.3 Anti-drug antibodies

Anti-drug antibodies were detected in 14.3 percent of dapiglutide-treated participants in the 13-week Phase 1b trial [6]. The clinical significance of these antibodies (whether they are neutralizing, whether they affect efficacy or safety) has not been reported. Formation of anti-drug antibodies is a known phenomenon with peptide

therapeutics and is monitored in all incretin drug development programs; clinically significant immunogenicity was not apparent from the reported weight-loss and safety data.

11.4 Theoretical safety considerations

Intestinal neoplasia: Chronic GLP-2R activation produces sustained intestinal epithelial proliferation. The theoretical concern that this trophic stimulus could promote intestinal neoplasia has been raised for all GLP-2R agonists, including teduglutide (which carries labeling regarding colorectal polyp surveillance). Long-term safety data for dapiglutide are limited to 28 weeks; the intestinal neoplasia question remains open and would require multi-year safety monitoring in any registration program.

Pancreatitis: GLP-1R agonists as a class have been associated with rare cases of acute pancreatitis, though large-scale outcomes trials (SUSTAIN, PIONEER, LEADER for semaglutide and liraglutide) have not demonstrated excess pancreatitis risk. No cases of pancreatitis have been reported with dapiglutide.

Medullary thyroid carcinoma: GLP-1R agonists produce thyroid C-cell tumors in rodents at supraphysiological doses. The relevance to humans is uncertain but has prompted labeling contraindications for semaglutide and liraglutide in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. No thyroid safety signals have been reported for dapiglutide in the limited clinical dataset.

11.5 Pregnancy and reproductive safety

No human pregnancy data exist for dapiglutide. The compound is investigational and is contraindicated in pregnancy by virtue of its development-stage status. Animal reproductive toxicology data have not been published.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative incretin-class or dual-mechanism agents against dapiglutide, evaluated against five competency standards: novelty, effect size (weight loss), promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal clinical alternatives in the obesity pharmacotherapy landscape and to clarify the scientific positioning of dapiglutide's dual GLP-1R/GLP-2R mechanism.

12.1 Semaglutide (Wegovy/Ozempic)

Mechanism: Selective GLP-1R agonist. Acylated GLP-1 analog with C18 fatty diacid modification and amino acid substitutions conferring DPP-4 resistance and extended half-life (approximately 168 hours).

Novelty: Low. Semaglutide is a second-generation GLP-1R monoagonist within an established class. The mechanism is well characterized and the compound is widely marketed.

Effect size: Substantial. The STEP program demonstrated 14.9 percent (STEP 1), 16.9 percent (STEP 5, 2 years), and up to 17.4 percent placebo-adjusted weight loss at 2.4 mg weekly subcutaneous [21]. Oral semaglutide (50 mg daily) produces approximately 15 percent weight loss in OASIS trials.

Promising potential: High. Approved in multiple jurisdictions for obesity (Wegovy) and type 2 diabetes (Ozempic). Dominant market position. Extensive cardiovascular outcomes data (SELECT trial) demonstrating 20 percent reduction in major adverse cardiovascular events [22].

Side-effect profile: Gastrointestinal adverse events predominate: nausea (approximately 44 percent), vomiting (approximately 24 percent), diarrhea (approximately 30 percent) in registration trials. These are generally mild-to-moderate and attenuate with continued dosing. Rare pancreatitis, gallbladder events, and retinopathy progression signals exist.

Overall validation: Very high. The most extensively validated weight-loss pharmacotherapy currently marketed, with Phase 3 efficacy, cardiovascular outcomes benefit, and several years of real-world safety data.

Comparison to dapiglutide: Semaglutide achieves greater weight loss (14 to 17 percent) than dapiglutide at comparable treatment durations, but lacks the GLP-2R-mediated intestinal barrier and anti-inflammatory activity that constitutes dapiglutide's mechanistic differentiation. Dapiglutide's 11.6 percent weight loss at 28 weeks in Phase 1b approaches but does not equal semaglutide's Phase 3 efficacy; higher doses or longer durations may close this gap. The key differentiating question is whether GLP-2R activation produces clinically meaningful anti-inflammatory benefits beyond what weight loss alone achieves.

12.2 Tirzepatide (Mounjaro/Zepbound)

Mechanism: Dual GLP-1R/GIP receptor agonist. A 39-amino-acid peptide with C20 fatty diacid modification activating both the GLP-1 receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor.

Novelty: Moderate. First-in-class dual GLP-1R/GIP agonist, a novel mechanism at the time of approval (2022).

Effect size: Very substantial. The SURMOUNT-1 trial demonstrated 20.9 percent weight loss at 15 mg versus 3.1 percent placebo at 72 weeks [23]. Head-to-head comparison with semaglutide (SURPASS-2) demonstrated superiority for HbA1c reduction and weight loss [24].

Promising potential: Very high. Approved for obesity (Zepbound) and type 2 diabetes (Mounjaro) in multiple jurisdictions. Extensive Phase 3 program. Cardiovascular outcomes trial (SURPASS-CVOT) ongoing.

Side-effect profile: Similar GI profile to semaglutide: nausea (approximately 29 percent at 15 mg), diarrhea (approximately 23 percent), vomiting (approximately 12 percent). Rates modestly lower than semaglutide in head-to-head comparison (SURMOUNT-5: 20.2 percent weight loss tirzepatide vs 13.7 percent semaglutide) [24].

Overall validation: Very high. Approved, marketed, with robust Phase 3 efficacy exceeding GLP-1R monoagonists.

Comparison to dapiglutide: Tirzepatide achieves substantially greater weight loss than dapiglutide at all reported timepoints and has the advantage of regulatory approval and extensive clinical validation. The mechanistic differentiation between the two dual agonists is fundamental: tirzepatide adds GIP receptor activation (enhancing insulinotropic and adipose tissue effects), while dapiglutide adds GLP-2R activation (intestinal barrier and anti-inflammatory effects). For patients whose obesity is associated with intestinal barrier dysfunction and low-grade endotoxemia, dapiglutide may offer theoretical advantages that tirzepatide does not; for maximal weight loss, tirzepatide is substantially more effective based on current data.

12.3 Survodutide (BI 456906)

Mechanism: Dual GLP-1R/glucagon receptor agonist. The glucagon receptor component promotes hepatic fat oxidation, thermogenesis, and amino acid catabolism, complementing GLP-1R-mediated appetite suppression.

Novelty: Moderate to high. First-in-class dual GLP-1R/glucagon agonist in late-stage development for obesity and metabolic dysfunction-associated steatohepatitis (MASH).

Effect size: Substantial. Phase 2 trial (SYNCHRONIZE-1) reported up to 18.7 percent weight loss at 48 weeks [25]. Phase 2 MASH trial demonstrated significant liver fat reduction and histological improvement.

Promising potential: High. Phase 3 program ongoing (SYNCHRONIZE-3 and SYNCHRONIZE-4 for obesity). Potential differentiation in MASH through hepatic glucagon effects.

Side-effect profile: Gastrointestinal adverse events similar to GLP-1R agonist class. Additional concern for glucagon-mediated hepatic aminotransferase elevation and potential for glucagon-driven hyperglycemia (though offset by GLP-1R insulinotropic activity).

Overall validation: Moderate. Phase 2 data published; Phase 3 ongoing. Not yet approved.

Comparison to dapiglutide: Both are dual-mechanism agents targeting obesity-associated comorbidities beyond weight loss alone. Survodutide targets liver pathology (MASH) through hepatic glucagon receptor activation; dapiglutide tar-

gets intestinal barrier dysfunction through GLP-2R activation. The mechanistic targets are complementary rather than competitive. Survodutide produces substantially greater weight loss (18.7 percent vs 11.6 percent) and is further advanced in clinical development.

12.4 Teduglutide (Gattex/Revestive)

Mechanism: Selective GLP-2R agonist. A GLP-2 analog with a single amino acid substitution (Ala2Gly) conferring DPP-4 resistance and extending half-life to approximately 2 to 3 hours. Administered once daily by subcutaneous injection.

Novelty: Low. Teduglutide is the reference selective GLP-2R agonist, approved since 2012.

Effect size: Not applicable for weight loss (teduglutide does not produce weight loss and is not indicated for obesity). For the intestinal insufficiency indication (short bowel syndrome), teduglutide reduces parenteral nutrition requirements by 20 to 100 percent in responders [26].

Promising potential: Established. Approved for short bowel syndrome-associated intestinal failure. Not in development for obesity or metabolic disease.

Side-effect profile: Abdominal pain, nausea, injection site reactions, stoma complications. Labeling includes recommendation for colorectal polyp surveillance due to the trophic effects of chronic GLP-2R activation.

Overall validation: Moderate for intestinal insufficiency (approved, established use). Not validated for metabolic or inflammatory indications.

Comparison to dapiglutide: Teduglutide provides the GLP-2R agonist component in isolation, without GLP-1R-mediated weight loss or metabolic effects. Dapiglutide combines both receptor activities in a single molecule with once-weekly dosing (vs daily for teduglutide). For research applications examining GLP-2R-mediated barrier repair, teduglutide serves as the reference selective agonist against which dapiglutide's GLP-2R contribution can be mechanistically parsed. Dapiglutide's advantage is the combined mechanism; teduglutide's advantage is regulatory approval and established clinical use.

12.5 Retatrutide (LY3437943)

Mechanism: Triple agonist at GLP-1R, GIP receptor, and glucagon receptor. A single acylated peptide activating three receptors simultaneously.

Novelty: High. First-in-class triple agonist, the most mechanistically complex incretin candidate in clinical development.

Effect size: Exceptional. Phase 2 trial reported up to 24.2 percent weight loss at 48 weeks (12 mg dose) [27]. This is the largest weight loss reported for any pharmacotherapy in a randomized clinical trial.

Promising potential: High. Phase 3 program (TRIUMPH) initiated by Eli Lilly. Expected regulatory submission pending Phase 3 completion.

Side-effect profile: Gastrointestinal events predominate (nausea, diarrhea, vomiting) at rates similar to or modestly higher than tirzepatide. Some hepatic enzyme elevations attributable to glucagon receptor activity [27].

Overall validation: Moderate. Phase 2 published with exceptional efficacy; Phase 3 ongoing. Not yet approved.

Comparison to dapaglutide: Retatrutide achieves approximately twice the weight loss of dapaglutide (24 percent vs 11.6 percent) and has a more complex multi-receptor mechanism. Dapaglutide's differentiation from retatrutide is the GLP-2R-mediated intestinal barrier and anti-inflammatory activity, which retatrutide does not possess. If obesity-associated intestinal barrier dysfunction and low-grade endotoxemia prove to be clinically important therapeutic targets beyond what weight loss alone addresses, dapaglutide may occupy a mechanistic niche that retatrutide cannot fill despite superior weight-loss efficacy.

12.6 Comparator summary

The five comparators span the current incretin therapeutics landscape from established monoagonists (semaglutide), through approved dual agonists (tirzepatide), to investigational dual agonists targeting different receptor pairs (survodutide) and triple agonists (retatrutide), with teduglutide representing the selective GLP-2R reference compound.

Dapiglutide occupies a unique mechanistic position as the only clinical-stage compound combining GLP-1R-mediated weight loss with GLP-2R-mediated intestinal barrier repair and anti-inflammatory activity. Its weight-loss efficacy (11.6 percent at 28 weeks, Phase 1b) is substantially below the current competitive benchmark (semaglutide 15 to 17 percent, tirzepatide 20 percent, retatrutide 24 percent). The compound's clinical differentiation therefore depends entirely on whether the GLP-2R component delivers clinically meaningful benefits (reduced systemic inflammation, improved intestinal barrier integrity, enhanced hepatic insulin sensitivity, reduced obesity-associated comorbidities) beyond what weight loss alone achieves. This question remains unanswered by the current clinical dataset and was intended to be addressed by the paused Phase 2b program.

The program pause reflects a rational assessment of competitive positioning: in a market where GLP-1R monoagonists, GLP-1R/GIP dual agonists, and GLP-1R/GIP/glucagon triple agonists all produce greater absolute weight loss, dapiglutide's path to registration requires demonstration of a qualitatively different benefit (anti-inflammatory, barrier-repair) that the weight-loss-superior competitors cannot match. The preclinical evidence for this differentiation is strong; the clinical evidence is preliminary and incomplete.

13. References

1. Zealand Pharma. Zealand Pharma announces successful outcome of Phase 1b clinical trial with GLP1-GLP2 dual receptor agonist, dapiglutide. GlobeNewswire. November 22, 2021.
2. Zealand Pharma. Zealand Pharma Presents Data from Phase 1 Trial of Dapiglutide at the 82nd Annual American Diabetes Association Scientific Sessions and Announces Dapiglutide to Move into Phase 2 Trial for Obesity. GlobeNewswire. June 6, 2022.
3. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* 2018;27(4):740-756.
4. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu Rev Physiol.* 2014;76:561-583.
5. Hjort SA, Skarbaliene J, Bhatt DK, et al. 1685-P: Dapiglutide is a dual agonist on human GLP-1- and GLP-2-receptors with a biased and prolonged signaling profile at the GLP-1R. *Diabetes.* 2024;73(Supplement_1):1685-P.
6. Zealand Pharma. Zealand Pharma announces positive topline results from 13-week Phase 1b multiple ascending dose clinical trial with GLP-1/GLP-2 receptor dual agonist dapiglutide. GlobeNewswire. September 9, 2024.
7. Zealand Pharma. Zealand Pharma announces positive topline results from 28-week Phase 1b trial with GLP-1/GLP-2 receptor dual agonist dapiglutide. GlobeNewswire. June 18, 2025.
8. Zealand Pharma. Zealand Pharma announces topline results from the mechanistic investigator-led DREAM trial with low doses of GLP-1/GLP-2 receptor dual agonist dapiglutide. GlobeNewswire. May 23, 2024.
9. Olsen MH, Heerwagen STR, Sonne N, et al. Dapiglutide, a dual GLP-1 and GLP-2 receptor agonist, for obesity: a randomised, double-blind, placebo-controlled parallel-group, proof-of-concept trial. *eClinicalMedicine.* 2026;73:103139.
10. Reiner J, Berlin P, Held J, et al. Dapiglutide, a novel dual GLP-1 and GLP-2 receptor agonist, attenuates intestinal insufficiency in a murine model of short bowel. *JPEN J Parenter Enteral Nutr.* 2022;46(5):1107-1118.

11. Reiner J, Thiery J, Held J, et al. The dual GLP-1 and GLP-2 receptor agonist dapiglutide promotes barrier function in murine short bowel. *Ann N Y Acad Sci.* 2022;1514(1):132-141.
12. Zealand Pharma. Dapiglutide (program paused). Zealand Pharma Pipeline. 2025. Available at: <https://www.zealandpharma.com/pipeline/dapiglutide-program-paused/>.
13. Dapiglutide. Wikipedia. Accessed May 2026. Molecular formula C192H302N46O57; molar mass 4166.793 g/mol.
14. Lau JL, Dunn MK. Therapeutic peptides: historical perspectives, current development trends, and future directions. *Bioorg Med Chem.* 2018;26(10):2700-2707.
15. Brubaker PL. Glucagon-like peptide-2 and the regulation of intestinal growth and function. *Compr Physiol.* 2018;8(3):1185-1210.
16. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev.* 2007;87(4):1409-1439.
17. Yaribeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. GLP-1 and GLP-2 orchestrate intestine integrity, gut microbiota, and immune system crosstalk. *Microorganisms.* 2022;10(10):2061.
18. Madsen KB, Askov-Hansen C, Naimi RM, et al. Metabolic and gut microbiome changes following GLP-1 or dual GLP-1/GLP-2 receptor agonist treatment in diet-induced obese mice. *Sci Rep.* 2019;9(1):15700.
19. Olsen MH, et al. 141-OR: Safety, tolerability, and clinical effects of dapiglutide, a once-weekly GLP-1R/GLP-2R agonist. *Diabetes.* 2025;74(Supplement_1):141-OR.
20. AbMole BioScience. Dapiglutide (ZP7570). Catalog No. M19693. CAS 2296814-85-0.
21. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;384(11):989-1002.
22. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med.* 2023;389(24):2221-2232.

23. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216.
 24. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515.
 25. Bossart M, Wagner M, Elvert R, et al. Effects on weight loss and glycemic control with the dual GLP-1/glucagon receptor agonist survodutide (BI 456906) in adults with overweight or obesity. *Lancet Diabetes Endocrinol*. 2023;11(12):903-913.
 26. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut*. 2011;60(7):902-914.
 27. Jastreboff AM, Kaplan LM, Frias JP, et al. Triple-hormone-receptor agonist retatrutide for obesity: a phase 2 trial. *N Engl J Med*. 2023;389(6):514-526.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Dapiglutide is an investigational compound not approved by any regulatory authority. The clinical dataset is limited to Phase 1 and early Phase 2 studies; efficacy and safety have not been established in registration-quality trials. Zealand Pharma has paused the development program. Investigators should obtain analytical confirmation of identity and purity on every lot of research-grade material.