

RESEARCH MONOGRAPH . COMPOUND PROFILE

Glepaglutide

A 39-amino-acid synthetic peptide analog of human glucagon-like peptide-2 engineered by Zealand Pharma with nine amino acid substitutions and a C-terminal hexalysine tail to enable depot formation, extended half-life, and ready-to-use liquid formulation for subcutaneous administration in short bowel syndrome.

DOCUMENT	KDC-MN-1414
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi ac bio l abs Research
COMPOUND CLASS	Long-acting glucagon-like peptide-2 (GLP-2) receptor agonist peptide analog

ABSTRACT

Glepaglutide (ZP1848) is a long-acting, synthetic peptide analog of human glucagon-like peptide-2 (GLP-2) developed by Zealand Pharma A/S (Soeborg, Denmark) for the treatment of short bowel syndrome (SBS) with intestinal failure in patients dependent on parenteral support. The compound comprises 39 amino acids and differs from native human GLP-2(1-33) by the incorporation of nine amino acid substitutions at positions 2, 3, 5, 8, 10, 11, 16, 24, and 28, together with a C-terminal amidated hexalysine tail ([Lys]6-NH₂) derived from Zealand Pharma's proprietary Structure Inducing Probe (SIP) technology. The substitutions confer resistance to dipeptidyl peptidase-4 (DPP-4) degradation, improved physicochemical stability enabling a ready-to-use aqueous liquid formulation, and formation of a subcutaneous depot from which the parent compound and its active C-terminally truncated metabolites (M1, 35 amino acids; M2, 34 amino acids) are slowly released into systemic circulation. The resulting effective half-life of approximately 50 to 124 hours in humans permits twice-weekly or once-weekly subcutaneous dosing, a substantial advance over the daily injection requirement of teduglutide (Gattex), the first-in-class approved GLP-2 analog. Glepaglutide binds and activates the GLP-2 receptor (GLP-2R), a class B G-protein-coupled receptor expressed on intestinal subepithelial myofibroblasts, enteroendocrine cells, and enteric neurons. Receptor activation triggers downstream release of intestinal growth mediators including insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and keratinocyte growth factor, resulting in crypt cell proliferation, villus elongation, inhibition of enterocyte apoptosis, enhanced intestinal barrier

function, increased mesenteric blood flow, and suppression of gastric acid hypersecretion and accelerated gastrointestinal motility. The net physiological effect is increased intestinal absorptive capacity for fluid, electrolytes, and macronutrients in patients with anatomically shortened bowel. Clinical development has progressed through Phase 1 healthy volunteer pharmacokinetic studies, a Phase 2 randomized crossover trial in 18 SBS patients published in *The Lancet Gastroenterology and Hepatology* (Naimi et al., 2019) demonstrating dose-dependent improvements in intestinal wet weight absorption and plasma citrulline, and the pivotal Phase 3 EASE-SBS 1 trial (NCT03690206), a multinational, double-blind, placebo-controlled study in 106 patients that met its primary endpoint of significant reduction in weekly parenteral support volume at 24 weeks (mean change minus 5.13 versus minus 2.85 liters per week for glepaglutide twice weekly versus placebo; P equals 0.0039). The compound received orphan drug designation from both the United States Food and Drug Administration and the European Medicines Agency. Zealand Pharma submitted a New Drug Application to the FDA in late 2023; in December 2024, the FDA issued a Complete Response Letter citing insufficient evidence to confirm efficacy and safety at the proposed marketed dose and recommending an additional confirmatory trial. A Marketing Authorization Application was submitted to the European Medicines Agency in June 2025, and Zealand Pharma plans an additional Phase 3 trial to support regulatory resubmission in the United States. The safety profile is consistent with the known GLP-2 class effects. The most frequent adverse events in clinical trials are injection site reactions, stoma complications (primarily swelling or enlargement of the stoma nipple), gastrointestinal events (nausea, vomiting, abdominal pain), peripheral edema,

fatigue, and headache. Anti-drug antibodies develop in a proportion of treated patients with a trend toward higher injection site reaction incidence in antibody-positive individuals, though no firm causal relationship has been established. The compound does not require reconstitution and is administered as a fixed-dose, ready-to-use subcutaneous injection via autoinjector, representing a practical advantage over lyophilized GLP-2 analogs requiring daily preparation. This monograph documents the chemistry, design rationale, and synthesis of glepaglutide; the GLP-2 receptor pharmacology and downstream intestinotrophic signaling; the comprehensive human pharmacokinetic profile including depot formation and metabolite characterization; the preclinical pharmacology in intestinal growth and inflammatory bowel disease models; the clinical evidence base from Phase 1 through Phase 3; sourcing and quality verification; reconstitution and handling; stack interaction considerations; adverse events and safety signals; and a comparative assessment of five GLP-2 receptor agonist candidates (teduglutide, apraglutide, dapiglutide, elsiglutide, and native GLP-2) against glepaglutide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Glepaglutide (recommended INN).

Development codes: ZP1848 (Zealand Pharma internal designation). The development code ZP1848 is the canonical identifier in the early pharmacology and Phase 1 literature.

Chemical Abstracts Service registry number: 914009-86-2.

Molecular formula: C₁₉₇H₃₂₅N₅₃O₅₅.

Structural designation: [Gly₂,Glu₃,Thr₅,Ser₈,Leu₁₀,Ala₁₁,Ala₁₆,Ala₂₄,Ala₂₈]-hGLP-2(1-33)-NH-[Lys]₆-NH₂ [1].

Peptide length: 39 amino acid residues (33 residues corresponding to the modified GLP-2 backbone plus a 6-residue C-terminal lysine tail).

Orphan drug designations: United States Food and Drug Administration (SBS); European Medicines Agency (SBS).

1.2 Structural class and chemistry

Glepaglutide belongs to the class of synthetic peptide analogs of human glucagon-like peptide-2, a 33-amino-acid proglucagon-derived intestinotrophic hormone. Native human GLP-2 (hGLP-2) is released from enteroendocrine L-cells of the distal ileum and colon in response to luminal nutrients and is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) cleavage at position 2, resulting in a circulating half-life of approximately 7 minutes [2].

Glepaglutide incorporates nine amino acid substitutions relative to native hGLP-2(1-33): glycine at position 2 (conferring DPP-4 resistance, as in teduglutide); glutamate at position 3; threonine at position 5; serine at position 8; leucine at position 10; and alanine at positions 11, 16, 24, and 28 [1]. These substitutions were selected through systematic structure-activity optimization to achieve high GLP-2 receptor

potency while simultaneously improving chemical and physical stability sufficient to permit a stable aqueous liquid formulation at physiological pH, a property not achievable with native hGLP-2 or teduglutide [1].

The C-terminal hexalysine tail ([Lys]6-NH₂) is appended to position 33 via amide bond and constitutes Zealand Pharma's Structure Inducing Probe (SIP) technology. The polylysine extension promotes intermolecular association and depot formation upon subcutaneous injection, slowing the release of active peptide into systemic circulation and thereby extending the effective half-life from hours to days [1, 3].

Physical properties: Glepaglutide is supplied as a clear, colorless to slightly yellow aqueous solution for subcutaneous injection. The ready-to-use liquid formulation is stable at refrigerated conditions (2 to 8 degrees Celsius) without reconstitution, representing a practical advance over lyophilized GLP-2 analogs.

1.3 Synthesis

Glepaglutide was synthesized batchwise by standard Fmoc (9-fluorenylmethyloxycarbonyl) solid-phase peptide synthesis [1]. The crude peptide was purified by preparative reverse-phase high-performance liquid chromatography. Identity of the purified material was confirmed by electrospray ionization mass spectrometry. The C-terminal hexalysine tail was reported to significantly improve synthesis yields by promoting peptide solubility during chain assembly and cleavage [1]. Industrial-scale manufacture employs good manufacturing practice (GMP) solid-phase peptide synthesis with subsequent formulation into the ready-to-use aqueous solution at the target concentration for autoinjector delivery. The compound is manufactured as the acetate salt for pharmaceutical formulation.

2. Abstract

Glepaglutide (ZP1848) is a long-acting, 39-amino-acid peptide analog of human glucagon-like peptide-2 developed by Zealand Pharma for the treatment of short bowel syndrome with intestinal failure. The compound activates the GLP-2 receptor to promote intestinal mucosal growth, enhance absorptive capacity, and reduce dependence on parenteral nutrition in patients with anatomically insufficient bowel length [4, 5].

The principal clinical application is the reduction of parenteral support requirements in adult patients with SBS who are dependent on intravenous fluid and nutrition supplementation. The pivotal Phase 3 EASE-SBS 1 trial demonstrated that glepaglutide 10 mg administered subcutaneously twice weekly significantly reduced weekly parenteral support volume compared to placebo over 24 weeks, with 102 of 106 enrolled patients completing the trial [5]. The magnitude of parenteral support reduction (mean change minus 5.13 liters per week versus minus 2.85 liters per week for placebo) was clinically meaningful and consistent with the class effect observed with teduglutide, the only currently approved GLP-2 analog for this indication.

The pharmacokinetic profile is distinguished by depot formation at the subcutaneous injection site, from which the parent compound and two active C-terminally truncated metabolites (M1 and M2) are slowly released. The effective half-life of approximately 50 to 124 hours enables twice-weekly dosing, a reduction in injection burden compared to the daily subcutaneous injection required for teduglutide [3, 6]. The compound is formulated as a ready-to-use aqueous solution in a prefilled autoinjector, eliminating the reconstitution step required for teduglutide.

Regulatory development has included submission of a New Drug Application to the FDA (2023), receipt of a Complete Response Letter (December 2024) citing insufficient confirmatory evidence at the proposed marketed dose, and submission of a Marketing Authorization Application to the European Medicines Agency (June 2025) [7, 8]. Zealand Pharma plans an additional Phase 3 trial to support United States regulatory resubmission.

Preclinical pharmacology extends beyond the SBS indication. Glepaglutide demonstrated anti-inflammatory and mucosal regenerative effects in a rat model of indomethacin-induced small intestinal inflammation, suggesting potential applicability to inflammatory bowel disease [9]. The compound significantly reduced inflammatory markers (alpha-1-acid glycoprotein, myeloperoxidase) and reversed intestinal shortening in both co-treatment and post-treatment regimens.

The safety profile is consistent with the GLP-2 agonist class. Principal adverse events are injection site reactions, stoma complications, gastrointestinal symptoms (nausea, vomiting, abdominal pain), peripheral edema, and fatigue. No unexpected serious safety signals have emerged from Phase 3 data. Anti-drug antibody formation occurs in a subset of patients but has not been associated with loss of efficacy or serious adverse events [5].

3. Discovery and Development History

3.1 Origin and rationale

The discovery of GLP-2 as an intestinotrophic hormone was reported by Drucker et al. in 1996, who demonstrated that exogenous GLP-2 administration produced significant small intestinal mucosal growth in mice [10]. This finding established the therapeutic rationale for GLP-2 analogs in conditions of intestinal insufficiency. The first clinical GLP-2 analog, teduglutide (formerly ALX-0600), was developed by NPS Pharmaceuticals (later acquired by Shire, then Takeda) and received FDA approval in 2012 as Gattex for the treatment of adult patients with SBS dependent on parenteral support [11].

Teduglutide demonstrated clinical proof-of-concept for the GLP-2 mechanism but had pharmacokinetic and formulation limitations: a half-life of only 2 to 3 hours requiring daily subcutaneous injection, and a lyophilized powder formulation requiring reconstitution before each administration [11]. These limitations represented an opportunity for next-generation GLP-2 analogs with extended duration of action and improved convenience.

3.2 Zealand Pharma peptide engineering

Zealand Pharma, a Danish biotechnology company specializing in peptide therapeutics, initiated the glepaglutide program to develop a long-acting GLP-2 analog with physicochemical properties enabling a stable liquid formulation. The design strategy employed systematic amino acid substitution across the GLP-2(1-33) backbone to identify variants with retained receptor potency, improved chemical stability (resistance to oxidation, deamidation, and aggregation), and enhanced physical stability in aqueous solution [1].

The C-terminal hexalysine SIP tail was a critical innovation: by promoting controlled intermolecular association at the injection site, the tail created a subcutaneous depot mechanism that extended the effective duration of action from hours to days without requiring lipidation, PEGylation, or albumin fusion strategies employed by other long-acting peptide programs [1].

3.3 Preclinical development

Preclinical studies in rats demonstrated that glepaglutide produced dose-dependent increases in small intestinal mass and length consistent with GLP-2 receptor activation [9, 12]. The intestinotrophic effect was associated with increased crypt depth, villus height, and mucosal cross-sectional area. Comparative preclinical pharmacology established that glepaglutide had lower receptor potency than teduglutide and apraglutide in vitro but achieved comparable or superior in vivo intestinotrophic activity at extended dosing intervals owing to its depot pharmacokinetics [12].

3.4 Clinical development timeline

Phase 1 studies in healthy volunteers characterized the pharmacokinetic profile, safety, and tolerability of single and multiple ascending subcutaneous doses of glepaglutide [3, 6]. These studies established the depot formation mechanism, characterized the M1 and M2 metabolite profile, and confirmed the extended half-life supporting twice-weekly or once-weekly dosing.

The Phase 2 trial (NCT02690025), published by Naimi et al. in *The Lancet Gastroenterology and Hepatology* in 2019, was a single-center, double-blind, randomized crossover study in 18 adult patients with SBS [4]. Patients received daily subcutaneous glepaglutide at 0.1, 1, or 10 mg for 3 weeks with 4 to 8 week washout periods between doses. The 1 mg and 10 mg doses produced significant improvements in intestinal wet weight absorption and significant increases in plasma citrulline (a biomarker of functional enterocyte mass), with trends toward increased villus height and crypt depth on intestinal biopsies [4, 13].

The Phase 3 EASE-SBS 1 trial (NCT03690206), a multinational, double-blind, placebo-controlled study conducted at 29 hospital centers across the United States, United Kingdom, Belgium, Canada, Denmark, France, Germany, the Netherlands, and Poland, enrolled 106 patients with SBS-IF dependent on parenteral support at least three days per week [5]. Patients were randomized equally to glepaglutide 10 mg twice weekly, glepaglutide 10 mg once weekly, or placebo for 24 weeks. Enrollment was completed in January 2022; positive topline results were announced in September 2022; and the full publication appeared in *Gastroenterology* in December 2024 [5].

The EASE-SBS 2 trial (NCT03905707) is an open-label, long-term safety and efficacy extension in which patients completing EASE-1 continued glepaglutide treatment for up to two years without placebo control [5].

3.5 Regulatory milestones

Zealand Pharma submitted a New Drug Application to the FDA in late 2023. In December 2024, the FDA issued a Complete Response Letter stating that the application did not meet requirements for substantial evidence of efficacy and safety at the proposed marketed dose, and recommended an additional confirmatory clinical trial [7]. In June 2025, Zealand Pharma submitted a Marketing Authorization Application to the European Medicines Agency based on the EASE-1 data package [8]. An additional Phase 3 trial is planned for initiation in 2025 to support both global regulatory submissions and United States resubmission.

4. Mechanism of Action

4.1 GLP-2 receptor biology

The glucagon-like peptide-2 receptor (GLP-2R) is a class B (secretin family) G-protein-coupled receptor encoded by the GLP2R gene. In the intestine, GLP-2R expression is localized to subepithelial myofibroblasts beneath the crypt-villus axis, enteroendocrine cells, and neurons of the submucosal and myenteric plexuses [14, 15]. Notably, the receptor is not expressed on the proliferating crypt epithelial cells themselves; the intestinotrophic action of GLP-2 is therefore indirect, mediated through paracrine release of growth factors from receptor-bearing stromal and neuronal cells [15].

4.2 Receptor activation and downstream signaling

Glepaglutide binds the GLP-2R at the orthosteric site with potent agonist activity, triggering Gs-coupled adenylyl cyclase activation and cyclic AMP generation in receptor-expressing cells [1, 12]. The downstream signaling cascade involves release of multiple paracrine growth mediators from subepithelial myofibroblasts and enteric neurons:

Insulin-like growth factor-1 (IGF-1): Released from subepithelial myofibroblasts in response to GLP-2R activation. IGF-1 acts on IGF-1 receptors expressed on crypt epithelial cells and Lgr5-positive intestinal stem cells, activating PI3K/Akt signaling, Wnt/beta-catenin pathway potentiation, and S-phase entry of stem and transit-amplifying progenitor cells [15, 16].

Epidermal growth factor (EGF) and ErbB ligands: Released from subepithelial myofibroblasts. ErbB receptor signaling in crypt cells promotes proliferation and survival through MAPK/ERK pathway activation [15].

Keratinocyte growth factor (KGF/FGF7): Promotes epithelial cell proliferation and differentiation in the crypt-villus axis.

4.3 Physiological effects on the intestinal mucosa

The composite downstream signaling produces several coordinated physiological effects:

Crypt cell proliferation: Increased mitotic activity in the crypt compartment through IGF-1R and ErbB-mediated stimulation of Lgr5-positive intestinal stem cells and transit-amplifying progenitor cells [16].

Villus elongation: Increased villus height resulting from enhanced cell production in the crypt and reduced apoptosis at the villus tip, expanding the absorptive surface area [4, 13].

Inhibition of enterocyte apoptosis: Reduced programmed cell death at the villus tip, prolonging the functional lifespan of mature absorptive enterocytes.

Enhanced barrier function: Strengthened tight junction integrity and reduced paracellular permeability, improving the intestinal barrier against luminal antigens and bacteria.

Increased mesenteric blood flow: GLP-2R activation on enteric neurons increases splanchnic perfusion, supporting nutrient uptake from the mucosal surface [13].

Suppression of gastric acid hypersecretion: Reduction of the compensatory gastric acid hypersecretion that occurs in SBS patients, decreasing fluid losses and improving absorption in the residual intestine.

Inhibition of accelerated motility: Slowing of intestinal transit through enteric neural mechanisms, increasing contact time between luminal contents and the absorptive epithelium.

4.4 GLP-1 receptor cross-reactivity

Pharmacological characterization has demonstrated that glepaglutide activates the GLP-1 receptor to a greater degree than teduglutide or apraglutide, though with substantially lower potency than at the GLP-2 receptor [12]. The clinical significance of this GLP-1R cross-reactivity at therapeutic doses has not been established; it may contribute to the gastrointestinal adverse events (nausea, vomiting) observed in clinical trials, which overlap with the known GLP-1R agonist adverse-event profile.

4.5 Anti-inflammatory mechanism

Beyond its intestinotrophic activity, GLP-2R activation suppresses intestinal inflammation through multiple pathways: reduction of proinflammatory cytokine release (TNF-alpha, IL-1beta, IL-6) from mucosal immune cells, decreased myeloperoxidase activity indicating reduced neutrophil infiltration, and promotion of mucosal regeneration in damaged epithelium [9]. These anti-inflammatory properties have been demonstrated for glepaglutide specifically in indomethacin-induced small intestinal inflammation models in rats, where the compound reversed intestinal shortening and normalized inflammatory markers without requiring pre-treatment [9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and depot formation

Glepaglutide is administered by subcutaneous injection. Upon injection, the hexalysine C-terminal tail promotes intermolecular association and formation of a subcutaneous depot at the injection site [1, 3]. The parent compound and its active metabolites are slowly released from this depot into systemic circulation, creating a pharmacokinetic profile characterized by extended absorption rather than rapid peak-and-trough kinetics.

The depot formation mechanism is the primary determinant of the pharmacokinetic profile. Unlike lipidated peptides (such as semaglutide, which achieves extended duration through albumin binding) or PEGylated peptides, glepaglutide achieves long action through physical depot formation at the injection site without covalent chemical modification to a carrier molecule [1].

5.2 Metabolite formation

Following subcutaneous injection, two principal active metabolites are formed within the depot by C-terminal proteolytic cleavage of the hexalysine tail: M1 (35 amino acids, resulting from removal of one lysine residue) and M2 (34 amino acids, resulting from removal of two lysine residues) [3, 6]. Both M1 and M2 retain GLP-2 receptor agonist activity. The pharmacokinetics of glepaglutide following subcutaneous dosing are primarily determined by the slow release of these metabolites from the subcutaneous depot rather than by systemic clearance of the parent compound [3].

5.3 Distribution

Detailed volume of distribution data from human studies have been reported in the Phase 1 pharmacokinetic characterization [3]. The compound distributes to the intestinal submucosal compartment where GLP-2R-expressing cells reside. Plasma

protein binding characteristics have not been published in detail but are expected to be moderate given the peptide nature of the compound.

5.4 Elimination and half-life

The estimated mean effective half-life for glepaglutide at the 5 mg and 10 mg subcutaneous doses was 124 hours (range 73 to 185 hours) and 88 hours (range 31 to 146 hours), respectively, in healthy volunteer studies [3]. This extended half-life supports twice-weekly dosing at the 10 mg clinical dose. By comparison, native GLP-2 has a half-life of approximately 7 minutes and teduglutide has a half-life of approximately 2 to 3 hours [2, 11].

Systemic clearance is primarily through proteolytic degradation, as expected for a peptide compound. Renal elimination of intact peptide is minimal.

5.5 Renal impairment

A dedicated pharmacokinetic study in subjects with renal impairment demonstrated that glepaglutide exposure was not meaningfully altered in mild, moderate, or severe renal impairment, and dose adjustment is not required on the basis of renal function [6]. This finding is consistent with the predominantly proteolytic (rather than renal) elimination pathway.

5.6 Route and dosing schedule

The clinical route of administration is subcutaneous injection via prefilled autoinjector. The Phase 3 program evaluated both twice-weekly and once-weekly dosing at the 10 mg fixed dose [5]. Twice-weekly dosing met the primary efficacy endpoint; once-weekly dosing showed numerically smaller reductions in parenteral support volume. The proposed marketed dose regimen is 10 mg subcutaneously twice weekly.

6. Preclinical Pharmacology

6.1 Intestintrophic activity in rodents

Glepaglutide produces dose-dependent increases in small intestinal mass, length, and mucosal thickness in rats following subcutaneous administration [9, 12]. The intestintrophic effect is associated with histologically confirmed increases in crypt depth, villus height, and epithelium height, consistent with stimulation of crypt cell proliferation and inhibition of villus tip apoptosis. The magnitude of intestinal growth at pharmacologically equivalent doses is comparable to teduglutide when dosing frequency is adjusted for the respective half-lives of the compounds [12].

6.2 Comparative preclinical pharmacology

In a head-to-head preclinical comparison of GLP-2 analogs in rats, apraglutide demonstrated lower clearance (0.27 mL/kg/min) and longer half-life (159 minutes) compared to glepaglutide (clearance 2.8 mL/kg/min, half-life 16 minutes in rats) and teduglutide (clearance 9.9 mL/kg/min, half-life 19 minutes in rats) [12]. However, the rat pharmacokinetic half-life of glepaglutide does not reflect the human depot-mediated effective half-life of 50 to 124 hours, because the depot formation mechanism operates differently across species and is dependent on the injection volume-to-body-mass ratio.

6.3 Inflammatory bowel disease model

Grondahl et al. (2023) evaluated glepaglutide in a rat model of indomethacin-induced small intestinal inflammation, a model system for inflammatory bowel disease [9]. Indomethacin produces reproducible small intestinal ulceration, shortening, and mucosal inflammation. Glepaglutide was tested in two regimens: co-treatment (administered simultaneously with indomethacin) and post-treatment (administered after inflammation was established).

In both regimens, glepaglutide significantly reduced the severity of small intestinal inflammation as measured by reversal of intestinal shortening, decreased plasma alpha-1-acid glycoprotein concentrations, and reduced tissue myeloperoxidase activity [9]. Simultaneously, glepaglutide produced significant increases in small intestinal mass, demonstrating preserved intestinotrophic activity in the inflamed intestine. The finding that post-treatment (rather than only pre-treatment or co-treatment) was effective is clinically relevant, as patients with IBD would present with established inflammation.

6.4 Bile acid and FGF-19 axis

A secondary analysis of the Phase 2 trial characterized the effects of glepaglutide on the bile acid-farnesoid X receptor-fibroblast growth factor 19 (FGF-19) axis in SBS patients [17]. Glepaglutide treatment increased plasma FGF-19 concentrations, consistent with enhanced ileal bile acid absorption and FXR activation. This finding supports the intestinotrophic mechanism and suggests additional metabolic benefits through improved enterohepatic bile acid cycling.

7. Clinical Evidence Base

7.1 Phase 1 healthy volunteer studies

Phase 1 studies characterized the pharmacokinetics, safety, and tolerability of glepaglutide in healthy subjects following single and multiple ascending subcutaneous doses [3]. These studies established the depot formation mechanism, confirmed the M1 and M2 metabolite profile, demonstrated dose-proportional exposure over the studied dose range, and identified the effective half-life supporting extended dosing intervals. The compound was well tolerated, with injection site reactions as the most common adverse event.

7.2 Phase 2 efficacy trial (Naimi et al., 2019)

The Phase 2 trial was a single-center, double-blind, randomized, crossover, dose-finding study conducted at Rigshospitalet, Copenhagen, Denmark, in 18 adult patients with SBS (with or without stoma) [4]. Patients received daily subcutaneous injections of glepaglutide at 0.1, 1, or 10 mg for 3 weeks in a crossover design with 4 to 8 week washout periods between treatment courses.

Primary outcomes were changes in intestinal wet weight absorption and urinary output measured by 72-hour metabolic balance studies. The 1 mg and 10 mg doses produced clinically meaningful improvements in intestinal absorption, with the 10 mg dose demonstrating the largest effect. Plasma citrulline, a validated biomarker of functional enterocyte mass, increased significantly in the 1 mg group (by 15.3 micromol/L; P equals 0.001) and the 10 mg group (by 15.6 micromol/L; P equals 0.001) [13].

Intestinal biopsies obtained before and after treatment showed trends toward increased villus height, crypt depth, and epithelium height in the 1 and 10 mg dose groups, though these histological endpoints did not achieve statistical significance in the small sample [13].

7.3 Phase 2 intestinal morphology and perfusion substudy

Naimi et al. (2023) reported a secondary analysis of the Phase 2 trial examining intestinal morphology and perfusion using quantitative fluorescence angiography with indocyanine green and Laser Speckle Contrast Imaging [13]. Glepaglutide did not significantly alter intestinal perfusion as measured at the end of the three-week treatment period. The authors noted that an acute-phase increase in intestinal perfusion at treatment initiation (consistent with the known GLP-2 effect on mesenteric blood flow) may have preceded the measurement timepoint [13].

7.4 Phase 3 EASE-SBS 1 trial

The pivotal EASE-SBS 1 trial (NCT03690206) was a multinational, randomized, double-blind, placebo-controlled, parallel-group study conducted at 29 hospital centers across nine countries [5]. A total of 106 patients with SBS-IF dependent on parenteral support at least three days per week were randomized equally to three arms: glepaglutide 10 mg subcutaneously twice weekly, glepaglutide 10 mg subcutaneously once weekly, or matching placebo.

The primary endpoint was the absolute change in weekly parenteral support volume from baseline to week 24, assessed by a standardized optimization protocol in which parenteral support prescriptions were adjusted according to prespecified hydration and nutritional criteria.

Primary efficacy results: Glepaglutide 10 mg twice weekly produced a mean reduction in weekly parenteral support volume of 5.13 liters per week versus 2.85 liters per week for placebo (difference minus 2.28 liters per week; P equals 0.0039) [5]. The once-weekly dosing arm showed a numerically smaller but non-statistically-significant reduction compared to placebo.

Completion rates were high: 102 of 106 patients (96 percent) completed the 24-week trial, and 96 continued into the open-label extension studies EASE-2 and EASE-3 [5].

The clinical relevance of the parenteral support reduction is substantial for SBS-IF patients, in whom parenteral nutrition dependency imposes catheter-related infection risk, hepatobiliary complications, impaired quality of life, and restricted mobility. Reductions in parenteral support volume and frequency reduce these risks proportionally.

7.5 EASE-SBS 2 and EASE-SBS 3 extension trials

The EASE-SBS 2 trial (NCT03905707) is a two-year, open-label extension assessing long-term safety and efficacy [5]. Patients from the EASE-1 placebo arm were re-randomized to glepaglutide once weekly or twice weekly. The trial does not include a placebo arm. Long-term safety data from this extension supported the regulatory submissions.

7.6 Transplantation substudy

Preliminary data from a substudy presented at the 2023 Transplantation congress reported that glepaglutide induced clinically meaningful improvements in patients with SBS-IF, including patients with prior intestinal transplantation or those being considered for transplant listing [18].

8. Sourcing and Quality Verification

Glepaglutide is not currently approved for commercial sale in any jurisdiction (as of the monograph revision date). The compound is available through the following channels:

Clinical trial supply: Zealand Pharma supplies glepaglutide through its clinical trial programs (EASE-SBS 1, 2, and 3) and any subsequent confirmatory trials. Access for clinical research is through the Zealand Pharma clinical development team.

Research-grade supply: Research-grade glepaglutide (as the acetate salt, ZP1848 acetate) is available from specialty peptide research suppliers including MedChemExpress and Invivochem at greater than 95 percent purity by HPLC. Supply is in milligram quantities for in vitro and preclinical research applications. Pricing reflects the complexity of solid-phase synthesis of a 39-amino-acid peptide.

Quality verification for research-grade material: Investigators should confirm:

- Reverse-phase HPLC purity (target greater than 95 percent area-percent)
- Electrospray ionization mass spectrometry confirmation of molecular weight (C197H325N53O55)
- Amino acid analysis to confirm composition consistent with the nine substitutions and hexalysine tail
- Peptide content determination (accounting for counter-ion, water, and residual solvent content)
- Endotoxin testing for any in vivo administration

Research-grade glepaglutide is appropriate for in vitro receptor pharmacology, cell-based assays, and preclinical animal studies. It should not be used for human administration outside of approved clinical trial protocols.

9. Reconstitution and Handling

9.1 Clinical formulation

Glepaglutide is formulated as a ready-to-use, clear aqueous solution for subcutaneous injection. This is a distinguishing feature of the compound: unlike teduglutide (which is supplied as a lyophilized powder requiring daily reconstitution with sterile water before each injection), glepaglutide requires no reconstitution step [1]. The prefilled autoinjector device delivers a fixed 10 mg dose. Storage is at refrigerated conditions (2 to 8 degrees Celsius). The formulation stability is a direct consequence of the amino acid substitutions selected during the design phase, which eliminated the oxidation-sensitive and aggregation-prone residues present in native GLP-2 and teduglutide [1].

9.2 Research-grade handling

Research-grade glepaglutide (acetate salt, lyophilized powder) should be reconstituted in sterile water, phosphate-buffered saline, or other physiological buffer at the desired concentration for the experimental application. Stock solutions should be prepared at concentrations appropriate for the planned dose range and aliquoted to avoid repeated freeze-thaw cycles.

Storage of the lyophilized research-grade material is at minus 20 degrees Celsius or below, desiccated, and protected from light. Reconstituted solutions should be stored at 2 to 8 degrees Celsius and used within 7 to 14 days, or aliquoted and stored at minus 20 degrees Celsius for longer-term use. Stability data for research-grade preparations should be confirmed experimentally for each lot.

9.3 Subcutaneous injection technique

Clinical administration is by subcutaneous injection into the abdomen, thigh, or upper arm. The injection should be rotated among sites to minimize injection site reaction accumulation. The autoinjector device is designed for patient self-administration after training.

10. Stack Interactions and Combinations

Glepaglutide is a peptide compound degraded by proteolysis rather than by cytochrome P450 enzymes. Conventional small-molecule drug-drug interactions mediated by CYP inhibition or induction are not expected. However, several pharmacological and physiological interactions warrant consideration:

Parenteral nutrition components: Glepaglutide is administered to patients receiving parenteral support. The reduction in parenteral support volume requires coordinated clinical management to avoid dehydration or electrolyte imbalance during the dose-optimization period. Parenteral support prescriptions should be adjusted according to standardized protocols monitoring urinary output, body weight, and serum electrolytes.

Oral medications with absorption dependent on intestinal surface area: The intestinotrophic effect of glepaglutide (increased villus height and absorptive surface area) may alter the absorption of concurrently administered oral medications. Narrow-therapeutic-index drugs (warfarin, digoxin, levothyroxine, immunosuppressants) should be monitored more closely during glepaglutide initiation and dose stabilization.

Other GLP-2 receptor agonists: Concurrent administration with teduglutide or apraglutide is pharmacologically redundant and has not been studied. The combination is not recommended.

GLP-1 receptor agonists: Given the reported mild GLP-1R cross-reactivity of glepaglutide, concurrent administration with GLP-1R agonists (semaglutide, liraglutide, tirzepatide) could theoretically produce additive gastrointestinal adverse effects (nausea, vomiting). The clinical relevance of this interaction in SBS patients is uncertain, as GLP-1R agonists are not commonly prescribed in this population.

Proton pump inhibitors and H2-receptor antagonists: GLP-2 suppresses gastric acid hypersecretion. Patients on concurrent acid-suppression therapy may experience additive reduction in gastric acid output. Clinical monitoring is appropriate but dose adjustment of acid-suppression therapy is not routinely required.

Immunosuppressants in transplant patients: SBS patients with prior intestinal transplant may be on chronic immunosuppression. No pharmacokinetic interaction is expected, but the immunological implications of enhanced mucosal growth in transplanted intestinal segments have not been fully characterized.

Octreotide and somatostatin analogs: Octreotide is sometimes used in SBS to reduce intestinal secretions. Somatostatin analogs suppress GLP-2 release from enteroendocrine L-cells; however, exogenous glepaglutide administration bypasses this feedback mechanism. The pharmacodynamic interaction between octreotide-mediated motility reduction and glepaglutide-mediated intestinotrophic growth has not been formally characterized.

11. Adverse Events and Safety

11.1 Common adverse events

The safety profile of glepaglutide across Phase 2 and Phase 3 trials is consistent with the known GLP-2 receptor agonist class effects [4, 5]:

- Injection site reactions (the most frequent adverse event; typically mild erythema, swelling, or pruritus at the injection site; incidence greater than 50 percent in Phase 2)
- Stoma complications (primarily swelling or enlargement of the stoma nipple; reported in approximately 72 percent of patients in Phase 2, lower in Phase 3)
- Nausea (reported in approximately 44 percent of Phase 2 patients, lower frequency in Phase 3)
- Abdominal pain (approximately 44 percent in Phase 2)
- Peripheral edema (approximately 56 percent in Phase 2)
- Vomiting (approximately 28 percent in Phase 2)
- Fatigue (approximately 33 percent in Phase 2)
- Abdominal distension (approximately 28 percent in Phase 2)
- Headache (reported in greater than 10 percent in Phase 3)
- Dizziness (approximately 28 percent in Phase 2)

The higher adverse event rates in Phase 2 compared to Phase 3 reflect the daily dosing protocol in Phase 2 (0.1, 1, and 10 mg daily for 3 weeks) versus the twice-weekly or once-weekly 10 mg dosing in Phase 3, as well as the smaller sample size and crossover design.

11.2 Injection site reactions and immunogenicity

Anti-drug antibodies developed in a proportion of glepaglutide-treated patients during Phase 3 [5]. A trend toward higher incidence of injection site reactions was observed in patients who became antibody-positive compared to those who remained antibody-negative. However, injection site reactions often preceded antibody detection, and some patients developed antibodies without notable injection

site reactions. No firm causal relationship between injection site reactions and anti-gepaglutide antibody development has been established [5]. Antibody formation has not been associated with loss of clinical efficacy or with serious adverse events.

11.3 Gastrointestinal events

The gastrointestinal adverse events (nausea, vomiting, abdominal pain, abdominal distension) are consistent with both GLP-2 class effects (increased intestinal growth and motility changes) and potential GLP-1R cross-reactivity. These events were predominantly mild to moderate, nonserious, and resolved during continued treatment [5].

11.4 Stoma complications

Stoma swelling or enlargement is a recognized class effect of GLP-2 agonists, reflecting the intestinotrophic action at the stoma site. This effect was managed clinically with stoma care optimization and did not require treatment discontinuation in the majority of cases [4, 5].

11.5 Potential for intestinal neoplasia

As a mitogenic growth factor promoting crypt cell proliferation, theoretical concern exists regarding the potential for GLP-2 agonists to promote intestinal neoplasia or accelerate growth of pre-existing intestinal polyps. This concern applies to the entire GLP-2 agonist class and is reflected in the teduglutide label, which recommends colonoscopic surveillance. Long-term surveillance data from gepaglutide extension trials have not identified a signal for increased neoplasia risk, but the duration of follow-up is limited [5].

11.6 Serious adverse events

The majority of adverse events in Phase 3 were nonserious and mild [5]. More adverse events were reported in gepaglutide groups (414 and 395 events in twice-weekly and once-weekly arms, respectively) compared to placebo (101 events), attributable primarily to mild injection site reactions. Serious adverse events were balanced across treatment groups and not attributed to the study drug in the published Phase 3 data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five GLP-2 receptor agonist candidates against glepaglutide, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators represent the principal GLP-2 receptor agonists with clinical or advanced preclinical development relevant to intestinal insufficiency indications.

12.1 Teduglutide (Gattex/Revestive)

Mechanism: GLP-2(1-33) analog with a single amino acid substitution (Gly2 replacing Ala2) conferring DPP-4 resistance. Daily subcutaneous injection at 0.05 mg/kg body weight [11].

Development trajectory: Developed by NPS Pharmaceuticals; FDA-approved December 2012 for adult SBS-IF; subsequently approved for pediatric SBS-IF. Currently marketed by Takeda as Gattex (US) and Revestive (EU). The compound is the first and only approved GLP-2 analog for SBS as of the monograph revision date.

Novelty: Low (as a current comparator). First-in-class with a simple single-amino-acid modification. The mechanism is established and well validated.

Effect size: In the pivotal STEPS trial, teduglutide 0.05 mg/kg/day produced a mean reduction in parenteral support volume of 4.4 liters per week versus 2.3 liters per week for placebo at 24 weeks [11]. Approximately 63 percent of teduglutide patients achieved a 20 percent or greater reduction in parenteral support volume. Effect size is broadly comparable to glepaglutide Phase 3 data.

Promising potential: High (as an approved, marketed product). Established revenue, post-marketing data, and clinical familiarity. However, the daily injection requirement, weight-based dosing, and reconstitution burden represent practical limitations that next-generation analogs address.

Side-effect profile: GLP-2 class effects (abdominal pain, nausea, stoma complications, injection site reactions). Additionally requires colonoscopic surveillance for colorectal polyps. Generally well tolerated.

Overall validation: Very high. FDA and EMA approved, post-marketing data spanning over a decade, extensive real-world clinical experience.

Comparison to glepaglutide: Teduglutide is the established standard of care. Glepaglutide offers reduced injection frequency (twice weekly versus daily), fixed dosing (versus weight-based), and ready-to-use formulation (versus reconstitution). Efficacy at 24 weeks appears comparable in magnitude across the respective pivotal trials, though indirect comparison across different trial populations carries methodological limitations.

12.2 Apraglutide (FE 203799, VectivBio/Ironwood)

Mechanism: Synthetic GLP-2 analog with very low systemic clearance and prolonged half-life (approximately 72 hours in humans), enabling once-weekly subcutaneous dosing [12, 19]. Retains full GLP-2R potency and selectivity comparable to native GLP-2.

Development trajectory: Originally developed by Ferring Pharmaceuticals; subsequently acquired by VectivBio (later acquired by Ironwood Pharmaceuticals in 2023). Phase 2 metabolic balance trials demonstrated improved fluid and energy absorption in SBS-IF patients [19]. Phase 3 development is ongoing.

Novelty: Moderate. Once-weekly dosing with retained full receptor potency represents an advance over teduglutide and a differentiation from glepaglutide (which also achieves extended dosing but through depot formation rather than intrinsic peptide stability).

Effect size: Phase 2 data demonstrated significant improvement in intestinal absorption. Comparative Phase 3 data against placebo or against teduglutide are not yet available in published form.

Promising potential: Moderate to high. Once-weekly dosing with high receptor selectivity (no GLP-1R cross-reactivity reported) is pharmacologically attractive. Phase 3 development is ongoing.

Side-effect profile: Phase 1 and Phase 2 data show a safety profile consistent with GLP-2 class effects. No unusual safety signals reported.

Overall validation: Moderate. Phase 2 data are positive; Phase 3 registration data are pending.

Comparison to glepaglutide: Apraglutide offers once-weekly dosing (versus twice-weekly for glepaglutide), higher GLP-2R selectivity (no GLP-1R cross-reactivity), and higher in vitro receptor potency. Glepaglutide offers the ready-to-use liquid formulation advantage and a more advanced regulatory dossier (NDA submitted, MAA submitted). The two compounds are direct competitors in the next-generation GLP-2 analog space.

12.3 Dapiglutide (Zealand Pharma)

Mechanism: Dual GLP-1/GLP-2 receptor agonist designed to provide simultaneous intestinotrophic (GLP-2) and metabolic/appetite (GLP-1) effects in a single molecule [20]. Developed by Zealand Pharma as a follow-on to glepaglutide.

Development trajectory: Phase 1b multiple ascending dose trial completed with positive topline results announced in September 2024 [20]. The 13-week trial demonstrated safety, tolerability, and pharmacokinetic profile consistent with once-weekly dosing. Clinical development targets include SBS and potentially other conditions where both GLP-1 and GLP-2 receptor activation would be beneficial.

Novelty: High. The dual GLP-1/GLP-2 agonist mechanism is a first-in-class concept that has not been previously validated clinically. It represents the most mechanistically innovative approach among the comparators.

Effect size: Phase 1b data demonstrate receptor activation biomarkers. Clinical efficacy data in SBS patients are not yet available.

Promising potential: Moderate. The compound is early in clinical development (Phase 1b completed). The theoretical rationale is strong, but clinical proof-of-concept in SBS patients is pending.

Side-effect profile: Phase 1b data reported tolerability consistent with the combined GLP-1/GLP-2 class effects. Full characterization awaits larger clinical trials.

Overall validation: Low. Phase 1b only. No efficacy data in the target patient population.

Comparison to glepaglutide: Dapiglutide represents Zealand Pharma's next-generation program that could supersede glepaglutide if clinical development is successful. However, glepaglutide has a substantially more advanced clinical dataset and regulatory dossier. The two compounds are sequentially positioned in Zealand Pharma's pipeline rather than directly competitive.

12.4 Elsiglutide (ZP1846, Zealand Pharma)

Mechanism: GLP-2 analog developed by Zealand Pharma for the prevention of chemotherapy-induced diarrhea. Unlike glepaglutide (which targets chronic intestinal insufficiency), elsiglutide targeted acute mucosal protection during cytotoxic chemotherapy [21].

Development trajectory: Zealand Pharma developed elsiglutide through Phase 2 clinical trials for prevention of chemotherapy-induced diarrhea in patients receiving irinotecan-based regimens. The program was licensed to Helsinn Group and subsequently returned to Zealand Pharma in 2017 [21]. The compound is not in active clinical development for any indication as of the monograph revision date.

Novelty: Low. The mechanism is conventional GLP-2R agonism applied to a different therapeutic context (acute mucosal protection rather than chronic intestinotrophic growth).

Effect size: Phase 2 results in chemotherapy-induced diarrhea did not demonstrate sufficient efficacy to support Phase 3 advancement.

Promising potential: Low. Development has been discontinued.

Side-effect profile: The compound was well tolerated in Phase 2 studies, with adverse events consistent with GLP-2 class effects.

Overall validation: Low. Development terminated after insufficient Phase 2 efficacy.

Comparison to glepaglutide: Elsiglutide and glepaglutide share the GLP-2R agonist mechanism and the Zealand Pharma peptide engineering platform but target different indications and have different pharmacokinetic profiles. Glepaglutide is the successful long-duration program from which the SBS development proceeded; elsiglutide represents an earlier, shorter-duration application that did not advance.

12.5 Native human GLP-2(1-33)

Mechanism: The endogenous 33-amino-acid hormone released from enteroendocrine L-cells of the distal ileum and colon. Activates the GLP-2R with full agonist potency and complete selectivity over other receptors [2, 10].

Development trajectory: Native GLP-2 was the proof-of-concept molecule studied by Drucker et al. (1996) and subsequently used in clinical proof-of-concept infusion studies in SBS patients by Jeppesen et al. (2001) [10, 22]. It has never been developed as a therapeutic product owing to its 7-minute half-life requiring continuous intravenous infusion.

Novelty: Not applicable (endogenous molecule, historical reference).

Effect size: Clinical infusion studies demonstrated significant improvements in intestinal absorption with continuous subcutaneous infusion at 400 micrograms three times daily, validating the GLP-2 mechanism for SBS treatment [22]. However, the impracticality of the dosing regimen prevented clinical development.

Promising potential: None as a therapeutic candidate. High as a research tool and reference standard for GLP-2R pharmacology.

Side-effect profile: Well tolerated in infusion studies. No adverse effects beyond GLP-2 class effects.

Overall validation: High as a proof-of-concept molecule. The clinical validation of native GLP-2 infusion established the therapeutic rationale for all subsequent GLP-2 analogs including glepaglutide.

Comparison to glepaglutide: Native GLP-2 is the parent molecule from which glepaglutide was derived through systematic peptide engineering. Glepaglutide retains the receptor pharmacology while achieving the pharmacokinetic and physicochemical properties necessary for practical clinical use.

12.6 Comparator summary

The five comparators occupy distinct positions in the GLP-2 receptor agonist landscape. **Teduglutide** is the approved standard of care with very high clinical validation but practical limitations in dosing frequency and formulation. **Apraglutide** is the principal next-generation competitor with once-weekly dosing and high receptor selectivity, but pending Phase 3 data. **Dapiglutide** represents the most mecha-

nistically novel approach (dual GLP-1/GLP-2 agonism) but is early in clinical development. **Elsiglutide** is a discontinued Zealand Pharma program in a different indication. **Native GLP-2** is the historical proof-of-concept molecule and research reference standard.

Glepaglutide occupies the position of the most clinically advanced next-generation GLP-2 analog, with completed Phase 3 data, regulatory submissions to both FDA and EMA, and a ready-to-use formulation in a prefilled autoinjector. Its principal clinical differentiation from teduglutide is the reduced injection frequency (twice weekly versus daily) and the elimination of reconstitution. Its principal competitive vulnerability relative to apraglutide is the twice-weekly (rather than once-weekly) dosing frequency and the mild GLP-1R cross-reactivity that may contribute to gastrointestinal adverse events. The FDA Complete Response Letter represents a regulatory setback that apraglutide may exploit if its Phase 3 program produces a positive first-cycle approval, though apraglutide's regulatory timeline is uncertain.

13. References

1. Larsen BD, Petersen JB, Poulsen SM, et al. Creating glepaglutide, the first long-acting GLP-2 analogue to enable a ready-to-use injection. *J Med Chem.* 2025;68(3):3134-3145.
2. Hartmann B, Harr MB, Jeppesen PB, et al. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. *J Clin Endocrinol Metab.* 2000;85(8):2884-2888.
3. Hvistendahl MK, Naimi RM, Enevoldsen LH, et al. Pharmacokinetics of glepaglutide, a long-acting glucagon-like peptide-2 analogue: a study in healthy subjects. *Clin Drug Investig.* 2022;42(12):1073-1083.
4. Naimi RM, Hvistendahl M, Enevoldsen LH, et al. Glepaglutide, a novel long-acting glucagon-like peptide-2 analogue, for patients with short bowel syndrome: a randomised phase 2 trial. *Lancet Gastroenterol Hepatol.* 2019;4(5):354-363.
5. Jeppesen PB, Gabe SM, Seidner DL, et al. Glepaglutide, a long-acting glucagon-like peptide-2 analogue, reduces parenteral support in patients with short bowel syndrome: a phase 3 randomized controlled trial. *Gastroenterology.* 2024;168(3):509-521.
6. Hvistendahl MK, Sonne DP, Hansen SH, et al. Pharmacokinetics, safety, and tolerability of glepaglutide, a long-acting GLP-2 analog, in subjects with renal impairment. *Clin Pharmacokinet.* 2023;62(4):589-599.
7. US Food and Drug Administration. Complete Response Letter for glepaglutide New Drug Application. December 19, 2024. Zealand Pharma press release, GlobeNewsWire.
8. Zealand Pharma. Zealand Pharma submits Marketing Authorization Application to the European Medicines Agency for glepaglutide in short bowel syndrome. Press release, GlobeNewsWire. June 2, 2025.
9. Grondahl MF, Keez NL, Karnov K, et al. Glepaglutide, a novel glucagon-like peptide-2 agonist, has anti-inflammatory and mucosal regenerative effects in an experimental model of inflammatory bowel disease in rats. *BMC*

Gastroenterol. 2023;23:88.

10. Drucker DJ, Erlich P, Asa SL, Bhargava AS. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci U S A*. 1996;93(15):7911-7916.
11. Jeppesen PB, Gilroy R, Pertkiewicz M, et al. 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.
12. Hargrove DM, Alagarsamy S, Croston G, et al. Pharmacological characterization of apraglutide, a novel long-acting peptidic glucagon-like peptide-2 agonist, for the treatment of short bowel syndrome. *J Pharmacol Exp Ther*. 2020;373(2):193-203.
13. Naimi RM, Hvistendahl MK, Enevoldsen LH, et al. Effects of glepaglutide, a long-acting glucagon-like peptide-2 analog, on intestinal morphology and perfusion in patients with short bowel syndrome: findings from a randomized phase 2 trial. *JPEN J Parenter Enteral Nutr*. 2023;47(4):516-525.
14. Munroe DG, Gupta AK, Kooshesh F, et al. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. *Proc Natl Acad Sci U S A*. 1999;96(4):1569-1573.
15. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu Rev Physiol*. 2014;76:561-583.
16. Dubeykovskaya ZA, Hunt D, Bhatt DK, et al. Glucagon-like peptide-2 stimulates S-phase entry of intestinal Lgr5+ stem cells. *Cell Mol Gastroenterol Hepatol*. 2022;13(6):1829-1847.
17. Hvistendahl MK, Naimi RM, Hansen SH, et al. Bile acid-farnesoid X receptor-fibroblast growth factor 19 axis in patients with short bowel syndrome: the randomized, glepaglutide phase 2 trial. *JPEN J Parenter Enteral Nutr*. 2021;45(8):1619-1630.
18. Zealand Pharma. Glepaglutide induces meaningful clinical improvement in patients with short bowel syndrome with intestinal failure. *Transplantation*. 2023;107(7S):66.
19. Eliasson J, Hvistendahl MK, Freund N, et al. Apraglutide, a novel once-weekly glucagon-like peptide-2 analog, improves intestinal fluid and energy absorption in patients with short bowel syndrome: an open-label phase 1 and 2 meta-

- bolic balance trial. JPEN J Parenter Enteral Nutr. 2022;46(8):1897-1906.
20. 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 dapaglutide. Press release, GlobeNewsWire. September 9, 2024.
21. Zealand Pharma. Zealand to regain control of elsiglutide. Press release, GlobeNewsWire. June 12, 2017.
22. Jeppesen PB, Hartmann B, Thulesen J, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology. 2001;120(4):806-815.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Glepaglutide is not approved by the United States Food and Drug Administration or the European Medicines Agency as of the monograph revision date. The compound is in late-stage clinical development for short bowel syndrome with intestinal failure. Investigators should consult their local regulatory authority and the sponsor (Zealand Pharma A/S) before any human research application. Research-grade material should be verified for identity and purity on every lot.