

RESEARCH MONOGRAPH . COMPOUND PROFILE

Teduglutide

A recombinant 33-amino-acid analog of human glucagon-like peptide-2 bearing a single glycine-for-alanine substitution at position 2 that confers resistance to dipeptidyl peptidase-IV degradation, developed by NPS Pharmaceuticals and approved for the treatment of short bowel syndrome with intestinal failure in adults and pediatric patients dependent on parenteral support.

DOCUMENT	KDC-MN-1415
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi ac biolabs Research
COMPOUND CLASS	Dipeptidyl peptidase-IV-resistant glucagon-like peptide-2 analog and GLP-2 receptor agonist

RESEARCH USE ONLY

ABSTRACT

Teduglutide is a recombinant analog of human glucagon-like peptide-2 (GLP-2) and the first GLP-2 receptor agonist approved for clinical use in the treatment of short bowel syndrome associated with intestinal failure (SBS-IF). The compound differs from native human GLP-2 by a single amino acid substitution: glycine replaces alanine at position 2 from the N-terminus, eliminating the dipeptidyl peptidase-IV (DPP-IV) cleavage site and extending the plasma elimination half-life from approximately 7 minutes (native GLP-2) to approximately 2 to 3 hours after subcutaneous administration [1, 2]. This modification preserves full agonist activity at the GLP-2 receptor (GLP-2R), a class B G-protein-coupled receptor expressed on intestinal subepithelial myofibroblasts, enteric neurons, and enteroendocrine cells, while enabling once-daily subcutaneous dosing at 0.05 mg/kg body weight.

The intestinotrophic actions of teduglutide are mediated through GLP-2R activation on subepithelial myofibroblasts, which triggers downstream release of insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and keratinocyte growth factor (KGF) [3, 4]. These paracrine mediators drive crypt cell proliferation, inhibit enterocyte apoptosis, increase villus height, enhance mucosal barrier function, slow gastric emptying, reduce gastric acid secretion, and increase mesenteric blood flow [5]. The composite physiological effect is an expansion of absorptive intestinal surface area and an improvement in the efficiency of fluid and nutrient absorption in patients with shortened bowel.

Clinical development centered on the pivotal Phase 3 STEPS trial (Study of Teduglutide Effectiveness in Parenteral Nutrition-Dependent Short-Bowel Syndrome Subjects), in which 86 adult SBS-IF patients were randomized to teduglutide 0.05 mg/kg/day or placebo for 24 weeks [6]. The primary endpoint (20 to 100 percent reduction in parenteral support volume at weeks 20 and 24) was met by 63 percent of teduglutide-treated patients compared to 30 percent of placebo-treated patients ($P = 0.002$). Three teduglutide-treated patients achieved complete enteral autonomy (full independence from parenteral support). Long-term extension studies (STEPS-2, STEPS-3) demonstrated sustained reductions in parenteral support requirements over 30 months or more, with additional patients achieving enteral autonomy on continued treatment [7, 8].

Teduglutide received European Commission marketing authorization as Revestive in August 2012, United States Food and Drug Administration (FDA) approval as Gattex in December 2012 for adult SBS-IF patients dependent on parenteral support, and FDA pediatric indication expansion in May 2019 for patients one year of age and older [9, 10]. The compound was developed by NPS Pharmaceuticals (subsequently acquired by Shire, then Takeda), with Takeda holding global commercial rights.

The principal safety concerns are the trophic effects of sustained GLP-2R stimulation on intestinal epithelium. Colorectal polyps have been reported in clinical trials and postmarketing surveillance at rates higher than placebo, necessitating colonoscopy within 6 months before treatment initiation, after 1 year of treatment, and every 5 years thereafter [11]. Intestinal obstruction, biliary and pancreatic disease, and fluid overload from increased intestinal absorption are additional monitored

risks. Common adverse events at the approved dose include abdominal pain (28 percent), nausea (26 percent), injection site reactions (26 percent), abdominal distension (17 percent), and headache (16 percent) [12].

This monograph reviews the chemistry, amino acid sequence, and DPP-IV resistance mechanism of teduglutide; the discovery of GLP-2 as an intestinotrophic factor and the development trajectory from preclinical demonstration through registration; the molecular pharmacology of GLP-2R signaling and downstream trophic mediators; the pharmacokinetic profile including absorption, distribution, metabolism, and elimination; the preclinical evidence in rodent models of SBS, mucositis, and colitis; the clinical evidence base across the STEPS trial series and pediatric studies; sourcing and quality verification considerations; reconstitution and handling; stack interaction considerations including effects on oral medication absorption; the adverse event and safety profile with emphasis on colorectal polyp risk; and a comparative assessment of five alternative GLP-2R agonists or intestinal trophic agents (glepaglutide, apraglutide, native GLP-2, growth hormone with glutamine, and somatropin) against teduglutide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Teduglutide.

Marketed names: Gattex (Takeda/Shire; United States, Canada), Revestive (Takeda; European Union, United Kingdom, Australia, other jurisdictions).

Development codes: ALX-0600 (NPS Pharmaceuticals/Allelix Biopharmaceuticals). The development code ALX-0600 is the canonical identifier in the early pharmacology literature and is found in initial Phase 1 and Phase 2 publications [1].

Chemical Abstracts Service registry number: 197922-42-2.

United States Adopted Name: Teduglutide. The compound is produced by recombinant DNA technology in *Escherichia coli* and is supplied as teduglutide [rDNA origin] for injection.

Molecular formula: C₁₆₄H₂₅₂N₄₄O₅₅S.

Molecular weight: 3752.1 g/mol (free peptide, calculated from amino acid composition).

1.2 Structural class and chemistry

Teduglutide is a 33-amino-acid peptide analog of human glucagon-like peptide-2 (GLP-2). Native human GLP-2 is a product of posttranslational processing of proglucagon in enteroendocrine L-cells of the distal ileum and colon. The amino acid sequence of teduglutide is identical to that of human GLP-2(1-33) with the sole exception of a glycine residue at position 2 in place of the native alanine [1, 2].

Amino acid sequence: H-His-Gly-Asp-Gly-Ser-Phe-Ser-Asp-Glu-Met-Asn-Thr-Ile-Leu-Asp-Asn-Leu-Ala-Ala-Arg-Asp-Phe-Ile-Asn-Trp-Leu-Ile-Gln-Thr-Lys-Ile-Thr-Asp-OH (single-letter code: HGDGSFSDEMNTILDNLAARDFINWLIQTKITD).

The glycine substitution at position 2 eliminates the DPP-IV cleavage site. Native GLP-2 is rapidly cleaved by DPP-IV at the Ala2-Asp3 bond, producing an inactive GLP-2(3-33) fragment and limiting the circulating half-life to approximately 7 minutes [2]. The substitution of glycine for alanine renders the peptide bond resistant to DPP-IV cleavage while preserving full agonist activity at the GLP-2 receptor. This strategy is analogous to the approach used for other DPP-IV-resistant incretin analogs but simpler than the acylation or PEGylation strategies employed for GLP-1 receptor agonists.

Physical properties: White to off-white lyophilized powder. Freely soluble in water upon reconstitution. The compound is supplied as a lyophilized powder in single-use vials containing 5 mg of teduglutide; after reconstitution with 0.5 mL of sterile water for injection, a 10 mg/mL solution is obtained from which up to 0.38 mL (3.8 mg) can be withdrawn for injection. The reconstituted solution is clear, colorless to light straw-colored, and free from visible particulates.

Stereochemistry: All amino acid residues are in the L-configuration, consistent with ribosomal biosynthesis in *E. coli* expression systems. The methionine residue at position 10 is susceptible to oxidation; oxidized teduglutide is a characterized degradation product and is monitored in stability-indicating assays.

1.3 Synthesis and manufacture

Teduglutide is manufactured by recombinant DNA technology in *E. coli*. The gene encoding the [Gly2]GLP-2(1-33) peptide sequence is expressed as a fusion protein, which is subsequently cleaved and purified to yield the active 33-amino-acid peptide [13]. The manufacturing process includes multiple chromatographic purification steps (ion exchange, hydrophobic interaction, and reverse-phase chromatography), endotoxin removal, sterile filtration, lyophilization, and final product characterization.

Quality control specifications include amino acid analysis, peptide mapping by reverse-phase high-performance liquid chromatography (RP-HPLC), mass spectrometry confirmation of molecular weight, size-exclusion chromatography for aggregate detection, endotoxin testing by *Limulus* amoebocyte lysate assay, sterility testing, and potency assay by GLP-2R activation in a cell-based bioassay. The product is supplied as a lyophilized powder in glass vials with a shelf life of 24 to 36 months when stored at 2 to 8 degrees Celsius.

Chemical synthesis of teduglutide by solid-phase peptide synthesis (Fmoc chemistry) has been demonstrated by multiple peptide synthesis suppliers for research-grade material. The 33-amino-acid length is within the routine capabilities of modern solid-phase synthesis, and research-grade teduglutide is available from chemical suppliers (Selleckchem, MedChemExpress, CPC Scientific, BOC Sciences, others) at greater than 95 percent purity by HPLC.

2. Abstract

Teduglutide ([Gly2]GLP-2, ALX-0600) is a dipeptidyl peptidase-IV-resistant analog of human glucagon-like peptide-2 and the first intestinotrophic hormone analog approved for clinical use. The compound acts as a full agonist at the GLP-2 receptor, a class B G-protein-coupled receptor expressed predominantly on intestinal subepithelial myofibroblasts and enteric neurons, to stimulate intestinal mucosal growth, enhance nutrient and fluid absorption, slow gastric emptying, reduce gastric acid secretion, and increase mesenteric blood flow [3, 4, 5].

The approved clinical indication is the treatment of adult and pediatric (one year of age and older) patients with short bowel syndrome who are dependent on parenteral support. Short bowel syndrome with intestinal failure (SBS-IF) is a condition resulting from extensive surgical resection of the small intestine (most commonly due to mesenteric ischemia, Crohn's disease, surgical complications, volvulus, or necrotizing enterocolitis in neonates), leaving insufficient absorptive surface to maintain fluid, electrolyte, and nutritional homeostasis by oral or enteral intake alone. Patients with SBS-IF require chronic parenteral nutrition (PN) and/or intravenous fluid support, which carries substantial morbidity including catheter-related bloodstream infections, liver disease, metabolic bone disease, and reduced quality of life [14].

The pivotal STEPS trial demonstrated that teduglutide 0.05 mg/kg/day administered subcutaneously for 24 weeks produced a clinically meaningful response (20 to 100 percent reduction in parenteral support volume) in 63 percent of treated patients versus 30 percent on placebo [6]. The STEPS-2 open-label extension demonstrated sustained benefit over an additional 24 months, with progressive reductions in parenteral support volume and additional patients achieving complete enteral autonomy [7]. The STEPS-3 long-term follow-up confirmed safety and continued efficacy over 30 months of continuous treatment [8].

Pharmacokinetics are characterized by rapid subcutaneous absorption (time to peak concentration 3 to 5 hours), a volume of distribution approximating blood volume, an elimination half-life of approximately 2 hours (range 1 to 6 hours depend-

ing on body weight), renal clearance as the primary elimination pathway, absolute bioavailability of approximately 88 percent, and no accumulation with once-daily dosing [15, 16].

The safety profile is dominated by gastrointestinal adverse events consistent with the trophic mechanism of action. The principal monitored risk is colorectal polyp formation: colonoscopy surveillance is required before initiation, after 1 year, and every 5 years during treatment [11]. The FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for Gattex to ensure that prescribers are informed of the neoplasia risk and colonoscopy monitoring requirements.

3. Discovery and Development History

3.1 Discovery of GLP-2 as an intestinotrophic factor

Glucagon-like peptide-2 was identified as a product of posttranslational processing of proglucagon in the 1980s, but its biological function remained obscure for approximately a decade after its initial characterization. The landmark discovery was made by Daniel Drucker and colleagues at the University of Toronto in 1996, who demonstrated that GLP-2 administration to mice produced striking increases in small intestinal mass, villus height, and crypt depth [17]. This observation was serendipitous in origin: Drucker's laboratory had noted that proglucagon-producing tumors (glucagonomas) induced intestinal growth in mice, and systematic investigation of the individual proglucagon-derived peptides identified GLP-2 as the intestinotrophic factor responsible for this effect.

The Drucker 1996 publication established GLP-2 as the first peptide hormone with potent and selective intestinotrophic activity. Exogenous GLP-2 administered to mice at pharmacological doses (2.5 micrograms twice daily intraperitoneally for 10 days) increased small intestinal weight by 40 to 50 percent, small intestinal length by 10 percent, and crypt-villus height by 30 to 40 percent, without affecting large intestinal, hepatic, or pancreatic mass [17]. This intestine-specific trophic activity was unprecedented among circulating peptide hormones and immediately established GLP-2 as a candidate therapeutic for intestinal insufficiency states.

3.2 GLP-2 receptor cloning and design of teduglutide

The GLP-2 receptor (GLP-2R) was cloned by Munroe, Drucker, and colleagues and reported in 1999 as a member of the class B (secretin family) of G-protein-coupled receptors, with expression restricted to the gastrointestinal tract (principally jejunum and ileum), the central nervous system (hypothalamus, hippocampus), and the lung [18]. The receptor signals through Gs-mediated cyclic AMP generation and through additional pathways including phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase cascades.

A critical observation for the development of a therapeutic GLP-2 analog was the demonstration that native GLP-2 is rapidly inactivated by DPP-IV, with a circulating half-life of approximately 7 minutes in humans [1, 2]. This rapid inactivation precluded direct therapeutic use without either continuous infusion or structural modification. Drucker and colleagues synthesized and tested over 100 GLP-2 analogs with modifications at the DPP-IV cleavage site and identified [Gly2]GLP-2 (subsequently designated ALX-0600, then teduglutide) as a lead compound that combined DPP-IV resistance with preserved full agonist activity at the GLP-2R [1, 13].

3.3 Preclinical development

Teduglutide was advanced through preclinical development by Allelix Biopharmaceuticals (Toronto, Canada), which subsequently merged into NPS Pharmaceuticals. Preclinical pharmacology studies demonstrated that teduglutide had prolonged biological activity compared to native GLP-2 and produced significant intestinotrophic effects in normal rodents and in surgical models of short bowel syndrome, including increases in intestinal length, intestinal weight, villus height, crypt depth, and crypt cell proliferation [1, 19].

Formal two-species (rat and dog), two-year toxicology studies demonstrated no evidence that sustained teduglutide administration promoted neoplastic transformation or tumorigenesis in normal animals [13]. However, in genetically or chemically sensitized rodent models of intestinal tumorigenesis (ApcMin mice, azoxymethane-treated rats), teduglutide enhanced tumor growth in some but not all studies, establishing the theoretical concern for trophic stimulation of pre-existing intestinal neoplasia that informs the clinical colonoscopy surveillance requirements [13].

3.4 Clinical development and registration

NPS Pharmaceuticals conducted Phase 1 pharmacokinetic and tolerability studies in healthy volunteers beginning in the early 2000s, followed by Phase 2 dose-finding studies in SBS-IF patients [15, 20]. The pivotal Phase 3 STEPS trial (NCT00798967) was conducted at multiple centers across North America and Europe and reported results in 2012 [6].

European Commission marketing authorization for Revestive was granted in August 2012. FDA approval for Gattex was granted on December 21, 2012, for the treatment of adult patients with SBS who are dependent on parenteral support [9]. The approval included a REMS program requiring prescriber certification and patient monitoring for intestinal neoplasia.

NPS Pharmaceuticals was acquired by Shire in 2015 for approximately 5.2 billion United States dollars, motivated largely by the Gattex/Revestive franchise. Shire was subsequently acquired by Takeda in 2019. Takeda holds global commercial rights to teduglutide. In 2007, NPS had granted Takeda GmbH (then Nycomed) the rights to develop and commercialize teduglutide outside the United States, Canada, Mexico, and Israel [10].

In May 2019, the FDA approved a supplemental New Drug Application extending the Gattex indication to pediatric patients one year of age and older with SBS who are dependent on parenteral support, based on data from two pediatric clinical trials [10, 21].

4. Mechanism of Action

Teduglutide is a full agonist at the glucagon-like peptide-2 receptor (GLP-2R). The mechanism of action is indirect: the GLP-2R is not expressed on the intestinal epithelial cells that are the functional targets of the trophic response, but rather on intestinal subepithelial myofibroblasts and enteric neurons in the lamina propria [3, 4]. GLP-2R activation on these cells triggers release of paracrine growth factors that act on adjacent epithelial stem and progenitor cells in the intestinal crypts.

4.1 GLP-2 receptor pharmacology

The GLP-2R is a class B (secretin family) G-protein-coupled receptor with seven transmembrane domains and a large extracellular N-terminal domain that participates in ligand binding [18]. The receptor is coupled to Gs, and agonist binding stimulates adenylyl cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP). Downstream signaling includes protein kinase A activation, phosphatidylinositol 3-kinase (PI3K)/Akt pathway activation, and extracellular signal-regulated kinase (ERK1/2) mitogen-activated protein kinase signaling [4, 22].

Teduglutide binds the GLP-2R with affinity comparable to native GLP-2 and produces full agonist responses in cAMP accumulation assays. Published radioligand binding studies report a K_i of approximately 0.5 to 2 nanomolar for displacement of [125 I]-GLP-2 from rat intestinal membrane preparations [1, 3]. Functional potency (EC_{50} for cAMP accumulation) in CHO cells expressing human GLP-2R is approximately 0.3 to 1.5 nanomolar, comparable to native GLP-2 [1, 22]. The glycine-for-alanine substitution at position 2 does not materially alter receptor binding affinity or maximal efficacy; it exclusively modifies metabolic stability.

Teduglutide is highly selective for the GLP-2R. Cross-reactivity with the structurally related GLP-1 receptor, glucagon receptor, GIP receptor, secretin receptor, and other class B GPCRs is negligible at pharmacologically relevant concentrations (greater than 1000-fold selectivity) [1, 3]. This selectivity is consistent with the high sequence divergence between GLP-2 and the other proglucagon-derived peptides in the receptor-binding N-terminal domain.

4.2 Downstream trophic mediators

The trophic effects of GLP-2R activation are mediated through at least three downstream paracrine pathways:

Insulin-like growth factor-1 (IGF-1). GLP-2R activation on intestinal subepithelial myofibroblasts stimulates IGF-1 mRNA expression and IGF-1 secretion through a PI3K/Akt-dependent mechanism [23, 24]. IGF-1 acts on IGF-1 receptors on intestinal crypt epithelial cells to stimulate proliferation. Genetic knockout of either IGF-1 or the intestinal epithelial IGF-1 receptor profoundly reduces GLP-2-induced crypt cell proliferation, microvillus lengthening, and barrier function improvement, establishing IGF-1 as a necessary mediator of the trophic response [23, 25].

Epidermal growth factor (EGF) and ErbB receptor ligands. GLP-2 treatment increases expression of ErbB receptor ligands (including EGF, amphiregulin, and epiregulin) in the intestinal mucosa. Inhibition of the ErbB family of receptor tyrosine kinases or knockout of the intestinal epithelial EGF receptor markedly impairs GLP-2-stimulated intestinal proliferation [4, 26]. The EGF and IGF-1 pathways appear to function cooperatively, with interdependent signaling required for the full trophic response.

Keratinocyte growth factor (KGF, FGF7). GLP-2R activation stimulates KGF release from subepithelial myofibroblasts, contributing to epithelial cell proliferation and mucosal repair [5, 27].

4.3 Composite physiological effects

The aggregate of GLP-2R-mediated paracrine signaling produces a composite of physiological effects relevant to intestinal adaptation in SBS-IF:

Crypt cell proliferation: increased mitotic rate in intestinal crypts, expanding the epithelial progenitor cell pool [17, 19]. **Inhibition of enterocyte apoptosis:** reduced programmed cell death in villus epithelial cells, extending epithelial cell lifespan and functional absorptive capacity [5]. **Villus height increase:** elongation of intestinal villi, increasing the absorptive surface area per unit length of bowel [17]. **Mucosal barrier enhancement:** improved tight junction integrity (upregulation of claudin-3, occludin, ZO-1) and reduced intestinal permeability [28]. **Slowed gastric emptying:** deceleration of gastric transit, increasing contact time between luminal nutrients and absorptive epithelium [29]. **Reduced gastric acid secretion:** decreased acid output, reducing luminal acid load and potentially improving nutrient diges-

tion efficiency [5]. Increased mesenteric blood flow: augmented splanchnic perfusion mediated by nitric oxide release from enteric neurons, supporting the metabolic demands of the expanded intestinal epithelium and enhancing nutrient delivery to the portal circulation [30]. Enhanced nutrient transporter expression: upregulation of SGLT1 (sodium-glucose cotransporter 1), GLUT2 (facilitative glucose transporter), and PepT1 (peptide transporter 1), increasing per-enterocyte absorptive capacity [31].

4.4 Relevance to short bowel syndrome

In patients with SBS-IF, the residual bowel undergoes a process of spontaneous intestinal adaptation over months to years following resection, characterized by villus hyperplasia, crypt deepening, and increased absorptive efficiency per unit length of remaining bowel. This adaptive process is partially GLP-2-dependent: endogenous GLP-2 secretion from L-cells in the residual ileum and colon contributes to the adaptive response. Teduglutide provides pharmacological augmentation of this endogenous adaptive mechanism, producing further mucosal expansion and absorptive improvement beyond the level achievable by spontaneous adaptation alone [14, 32].

The presence of residual colon in continuity with the small bowel is a positive predictor of teduglutide response, consistent with the colonic expression of GLP-2R and the contribution of colonic L-cell GLP-2 secretion to the trophic environment [6, 33].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Teduglutide is administered exclusively by subcutaneous injection. The absolute bioavailability after subcutaneous administration is approximately 88 percent (range 87 plus or minus 14 percent), reflecting efficient absorption from the subcutaneous depot [15, 16]. Time to maximum plasma concentration (T_{max}) is 3 to 5 hours after subcutaneous injection, with some variability by injection site (abdomen, thigh, arm) [16].

The compound is not orally bioavailable. As a 33-amino-acid peptide, teduglutide is subject to proteolytic degradation in the gastrointestinal tract and does not achieve systemic exposure after oral administration.

5.2 Distribution

The volume of distribution of teduglutide is approximately 103 mL/kg (approximately 7 to 8 liters in a 70-kilogram adult), consistent with distribution into the extracellular fluid compartment with limited tissue partitioning [15, 16]. Protein binding has not been formally characterized but is expected to be low for a hydrophilic peptide of this size. The compound does not cross the blood-brain barrier in significant quantities at therapeutic doses.

5.3 Metabolism and elimination

Teduglutide is not metabolized by hepatic cytochrome P450 enzymes. The compound is cleared primarily by the kidneys through glomerular filtration and proteolytic degradation. The terminal elimination half-life is approximately 2 hours (range 0.9 to 5.5 hours), with body weight as the principal determinant of half-life variability: lighter patients have shorter half-lives and heavier patients have longer half-lives [15, 16].

In the population pharmacokinetic model of Marier et al. (2010), a one-compartment model with first-order absorption and site-specific absorption rate constants for abdomen, arm, and thigh described the data adequately in healthy subjects, SBS patients, and Crohn's disease patients [16]. Renal clearance is the dominant elimination pathway; the compound is not a substrate of hepatic drug-metabolizing enzymes, and hepatic impairment does not materially alter teduglutide pharmacokinetics.

No accumulation of teduglutide was observed following repeated once-daily subcutaneous administrations, consistent with the short elimination half-life relative to the 24-hour dosing interval [15].

5.4 Special populations

Renal impairment: In subjects with moderate and severe renal impairment (creatinine clearance less than 50 mL/min), teduglutide exposure (AUC) is increased approximately 2-fold compared to subjects with normal renal function. End-stage renal disease patients not on dialysis showed approximately 3-fold higher exposure. Dose reduction to 0.025 mg/kg/day is recommended for patients with moderate to severe renal impairment [12].

Hepatic impairment: No clinically significant effect on teduglutide pharmacokinetics has been observed in patients with hepatic impairment. Given the proteolytic rather than hepatic metabolic route, significant alteration is not expected.

Pediatric patients: Population pharmacokinetic analysis in pediatric SBS patients aged 1 to 17 years supported the same weight-based dose of 0.05 mg/kg/day as in adults [21].

Elderly: No age-related pharmacokinetic differences have been identified in the adult population pharmacokinetic analyses.

5.5 Pharmacodynamic biomarkers

Plasma citrulline concentration is the principal pharmacodynamic biomarker for teduglutide activity. Citrulline is produced almost exclusively by enterocytes from glutamine metabolism; plasma citrulline concentration correlates with functional enterocyte mass [34]. Teduglutide treatment produces dose-dependent and time-dependent increases in plasma citrulline, with increases of 30 to 80 percent observed

over 12 to 24 weeks of treatment at the 0.05 mg/kg/day dose [6, 20]. Citrulline increases correlate with clinical response (reduction in parenteral support requirements) and serve as an early indicator of intestinal adaptation.

5.6 Routes of administration

Teduglutide is approved for subcutaneous injection only. Recommended injection sites include the thigh, arm, and the four quadrants of the abdomen, with rotation of injection sites recommended [12]. The compound should not be administered intravenously or intramuscularly.

6. Preclinical Pharmacology

6.1 Intestinotrophic activity in normal animals

The foundational preclinical pharmacology of GLP-2 and teduglutide was established in the Drucker laboratory at the University of Toronto. Native GLP-2 administered to normal mice produced dose-dependent increases in small intestinal weight (40 to 50 percent above vehicle), crypt depth (30 percent increase), villus height (25 to 35 percent increase), and epithelial cell proliferation as measured by bromodeoxyuridine incorporation [17]. Teduglutide ([Gly2]GLP-2) produced equivalent or greater effects at lower doses owing to the extended half-life, with once-daily subcutaneous dosing sufficient to produce maximal intestinotrophic effects whereas native GLP-2 required twice-daily administration [1, 19].

The intestinotrophic activity was restricted to the gastrointestinal tract: no significant trophic effects on liver, pancreas, kidney, or other extra-intestinal organs were observed at pharmacologically active doses, consistent with the tissue-restricted expression of the GLP-2R [17, 19].

6.2 Short bowel syndrome models

In rat models of massive small bowel resection (75 to 90 percent resection), teduglutide administration beginning at the time of resection or in the chronic post-resection period produced significant adaptation responses: increased remnant intestinal weight, villus height, crypt depth, mucosal DNA and protein content, and functional nutrient absorption as measured by D-xylose absorption tests [32, 35]. The Scott et al. (1998) rat model and the Martin et al. (2004) parenterally fed rat model of short bowel syndrome demonstrated that GLP-2 analog administration enhanced structural and functional adaptation of the remnant intestine [35, 36]. The Burrin et al. (2000) neonatal piglet model demonstrated that GLP-2 stimulated intestinal growth in premature total parenteral nutrition-fed piglets by suppressing proteolysis and apoptosis [37].

6.3 Models of intestinal injury and inflammation

Teduglutide demonstrated protective and reparative activity in multiple rodent models of intestinal injury: indomethacin-induced enteritis, 5-fluorouracil-induced mucositis, dextran sulfate sodium-induced colitis, radiation enteritis, and total parenteral nutrition-induced mucosal atrophy [38, 39, 40]. In the radiation injury model, Booth et al. (2004) demonstrated that teduglutide protected small intestinal stem cells from radiation damage, preserving the regenerative capacity of the crypt compartment [41]. In the colitis model, teduglutide reduced the severity of colonic injury and accelerated mucosal repair [40].

6.4 Carcinogenicity and tumor models

Formal two-year carcinogenicity studies in rats and mice at doses up to 50 mg/kg/day (approximately 100-fold the human dose on a mg/kg basis) did not demonstrate increased incidence of neoplasia in normal animals [13]. However, in genetically predisposed models (ApcMin mice, which carry a heterozygous loss-of-function mutation in the Apc tumor suppressor gene), teduglutide treatment increased the number and size of intestinal adenomas in some studies [13]. In chemically induced tumor models (azoxymethane-treated rats), results were inconsistent: some studies demonstrated enhanced tumor growth and others did not. These findings established the preclinical basis for the clinical concern regarding trophic stimulation of pre-existing intestinal neoplasia and informed the colonoscopy surveillance requirements in the approved prescribing information.

6.5 Mesenteric blood flow studies

Guan et al. (2003) demonstrated in total parenteral nutrition-fed piglets that GLP-2-mediated upregulation of intestinal blood flow and glucose uptake was nitric oxide-dependent, establishing the role of enteric neuronal nitric oxide synthase as a downstream mediator of the vasodilatory response to GLP-2R activation [30]. Bremholm et al. (2009) extended this finding to humans, demonstrating that GLP-2 infusion increased superior mesenteric artery blood flow in healthy subjects [42].

7. Clinical Evidence Base

7.1 Phase 2 proof-of-concept studies

The first human efficacy data were reported by Jeppesen et al. (2005) in short bowel syndrome patients [20]. In a randomized Phase 2 study, 16 parenteral-nutrition-dependent SBS patients received teduglutide at 0.03, 0.10, or 0.15 mg/kg/day subcutaneously for 21 days in a crossover design. All active doses produced significant increases in intestinal wet weight absorption; the 0.10 mg/kg/day dose produced the largest effect but was associated with more gastrointestinal adverse events (abdominal pain, nausea). These findings supported selection of 0.05 mg/kg/day as the Phase 3 dose, balancing efficacy and tolerability [20].

Jeppesen et al. (2001) had previously demonstrated in an open-label study that native GLP-2 administered by subcutaneous injection three times daily for 35 days improved nutrient absorption and nutritional status in short-bowel patients with no colon [43]. This study provided the proof-of-concept for GLP-2-based intestinal rehabilitation that motivated the teduglutide clinical program.

7.2 Pivotal Phase 3 STEPS trial

The STEPS trial (NCT00798967; Jeppesen et al. 2012) was the pivotal registration study. Eighty-six adult SBS-IF patients dependent on parenteral support for at least 12 months were randomized 1:1 to teduglutide 0.05 mg/kg/day or placebo administered subcutaneously once daily for 24 weeks [6]. All patients completed an optimization and stabilization run-in period to ensure stable parenteral nutrition requirements before randomization.

Primary endpoint: Proportion of patients achieving a 20 to 100 percent reduction from baseline in weekly parenteral support volume at both weeks 20 and 24. Result: 63 percent of teduglutide-treated patients met the primary endpoint versus 30 percent of placebo-treated patients ($P = 0.002$) [6].

Key secondary endpoints: Mean absolute reduction in parenteral support volume was 4.4 liters per week with teduglutide versus 2.3 liters per week with placebo. Three patients (7 percent) in the teduglutide arm achieved complete inde-

pendence from parenteral support (enteral autonomy) versus none in the placebo arm [6].

Subgroup analyses: Efficacy was observed across subgroups defined by intestinal anatomy (jejunostomy versus jejuno-colonic anastomosis versus jejuno-ileal-colonic anastomosis), though patients with colon in continuity showed numerically greater absolute volume reductions, consistent with the colonic contribution to GLP-2R-mediated absorptive adaptation [6, 33].

7.3 STEPS-2 and STEPS-3 extension studies

The STEPS-2 open-label extension (NCT00930644) enrolled patients completing the STEPS trial and additional new patients and provided teduglutide 0.05 mg/kg/day for up to 24 additional months [7]. Patients who had received teduglutide in STEPS continued to show progressive additional reductions in parenteral support volume through 30 months of cumulative treatment. Patients who crossed over from placebo showed responses comparable to the original teduglutide arm within 24 weeks.

The STEPS-3 long-term safety extension confirmed sustained safety and efficacy over 30 months of cumulative treatment [8]. Pooled analysis of patients across the STEPS trial series demonstrated that enteral autonomy and greater numbers of days off parenteral support per week tended to occur in patients with lower baseline parenteral support requirements and in patients with noninflammatory bowel disease as the underlying cause of SBS-IF [33].

7.4 Pediatric clinical evidence

Two clinical trials evaluated teduglutide in pediatric SBS-IF patients. The Kocoshis et al. (2020) Phase 3 study in children aged 1 to 17 years demonstrated reductions in parenteral support volume comparable to those observed in adult studies, with 12 of 59 patients (20.3 percent) achieving enteral autonomy during the 24-week treatment period [21]. Safety findings were consistent with the adult profile, with vomiting (51.7 percent), pyrexia (43.8 percent), upper respiratory tract infection (41.6 percent), and cough (33.7 percent) being the most frequently reported adverse events [21, 44]. The pediatric data supported the FDA supplemental approval in May 2019 extending the Gattex indication to patients one year of age and older [10].

7.5 Real-world evidence and long-term data

Multiple real-world registries and observational cohort studies have confirmed the clinical trial findings in broader patient populations. A multinational SBS-IF registry demonstrated that patients treated with teduglutide achieved greater reductions in parenteral support volume compared to untreated patients, with treatment effects consistent across geographic regions, underlying disease etiologies, and remnant bowel anatomy configurations [45].

Long-term real-world data extending beyond 5 years of continuous treatment have demonstrated sustained efficacy without evidence of tachyphylaxis, supporting the durability of the intestinal adaptive response to chronic GLP-2R agonism [46]. During 5-year follow-up, no new colorectal cancer cases were reported in patients treated or never treated with teduglutide, though ever-treated patients had more new or worsening polyps than never-treated patients [46].

7.6 Clinical meaningfulness

The clinical meaningfulness of reductions in parenteral nutrition requirements is well established: each liter per week reduction in parenteral support translates to reduced catheter-connection time (typically 1 to 2 fewer infusion days per week), reduced metabolic complications of parenteral nutrition (hepatic steatosis, cholestasis, catheter-related bloodstream infections, bone disease, renal impairment), and improved patient quality of life [14]. Complete enteral autonomy, when achieved, eliminates the infection risk, thrombotic risk, and quality-of-life burden of long-term central venous access.

8. Sourcing and Quality Verification

Pharmaceutical-grade teduglutide (Gattex brand in the United States and Canada, Revestive brand in the European Union and other jurisdictions) is the approved therapeutic formulation and is supplied as a single-use vial containing 5 mg of lyophilized teduglutide for reconstitution with the supplied prefilled syringe of sterile water. The pharmaceutical formulation is available through specialty pharmacy distribution in the United States and through hospital and community pharmacies in European Union jurisdictions. The annual cost of therapy in the United States is approximately 300,000 to 400,000 United States dollars (list price prior to rebates and patient assistance programs), reflecting the orphan drug and rare disease pricing structure.

Research-grade teduglutide is supplied by multiple peptide synthesis and pharmaceutical research suppliers (Selleckchem, MedChemExpress, CPC Scientific, BOC Sciences, Bachem, Creative Peptides, others) at greater than 95 percent purity by HPLC. Supply is in milligram quantities as the acetate salt or trifluoroacetate salt of the free peptide. Research-grade teduglutide is produced by solid-phase peptide synthesis (Fmoc chemistry) rather than by recombinant expression. Pricing for research-grade material is in the range of 200 to 500 United States dollars per milligram at typical research scales.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reverse-phase high-performance liquid chromatography area-percent purity (C18 column, acetonitrile/water gradient with 0.1 percent trifluoroacetic acid), targeting greater than 95 percent
- Mass spectrometry confirmation of molecular weight (expected [M+H]⁺ approximately 3753 Da by electrospray ionization or MALDI-TOF)
- Amino acid analysis to confirm sequence composition, particularly verifying the glycine-for-alanine substitution at position 2
- Peptide content determination by amino acid analysis or nitrogen analysis (lyophilized peptides typically contain 60 to 80 percent peptide content by weight owing to counterion, water, and salt contributions)

- Endotoxin testing by Limulus amoebocyte lysate assay for any material intended for in vivo administration (target: less than 0.5 EU/mg)
- Methionine oxidation assessment by RP-HPLC or mass spectrometry (oxidized Met10 is a common degradation product)

The distinction between recombinant (pharmaceutical-grade) and synthetic (research-grade) teduglutide is operationally important: recombinant material may carry different impurity profiles (host cell proteins, endotoxin, DNA) compared to synthetic material (deletion peptides, truncation products, counterion residues). Investigators should select the appropriate grade for their specific application.

9. Reconstitution and Handling

9.1 Pharmaceutical formulation reconstitution

The marketed Gattex/Revestive formulation is supplied as a kit containing a single-use vial of lyophilized teduglutide (5 mg) and a prefilled syringe of 0.5 mL sterile water for injection [12]. Reconstitution proceeds as follows:

1. Remove one vial of teduglutide and one prefilled syringe of sterile water for injection from refrigerated storage and allow to equilibrate to room temperature.
2. Inject the full 0.5 mL of sterile water into the vial containing the lyophilized powder.
3. Allow the vial to stand for 30 seconds, then gently roll the vial between the palms of the hands for 15 seconds. Do not shake.
4. Allow the reconstituted solution to stand for 2 minutes. Inspect for undissolved powder. If undissolved material remains, gently roll again until fully dissolved. Do not use if the product remains undissolved after a second attempt.
5. Inspect the reconstituted solution: it should be clear, colorless to light straw-colored, and free from visible particulates. Discard if discolored or if particulates are observed.
6. Withdraw up to 0.38 mL (3.8 mg) for subcutaneous injection based on the patient's prescribed dose (0.05 mg/kg body weight).

9.2 Storage conditions

Lyophilized vials are stored at 2 to 8 degrees Celsius (refrigerated). Do not freeze. The reconstituted solution must be administered within 3 hours and should be stored at room temperature during this period [12]. Teduglutide does not contain preservatives and is for single use only. Discard any unused portion.

9.3 Research-grade reconstitution

For research applications, lyophilized teduglutide is reconstituted in sterile water, phosphate-buffered saline (pH 7.4), or 10 mM histidine buffer (pH 6.0 to 7.0) at concentrations of 1 to 10 mg/mL. The peptide is freely soluble in aqueous solutions at physiological pH. Stock solutions for in vivo studies should be prepared fresh or aliquoted and stored at minus 20 degrees Celsius for up to 3 months; repeated freeze-thaw cycles (more than 3) should be avoided. For in vitro cell-based assays, concentrated stock solutions (1 to 10 mM in aqueous buffer) are diluted into culture medium immediately before use. Lyophilized research-grade peptide should be stored at minus 20 degrees Celsius or below, protected from moisture.

9.4 Injection technique

The subcutaneous injection is administered into the abdomen (preferred), thigh, or upper arm, rotating injection sites with each dose. The injection volume is typically 0.1 to 0.4 mL depending on patient weight and the dose calculation. The compound should not be administered intravenously or intramuscularly.

10. Stack Interactions and Combinations

Teduglutide is a peptide therapeutic that does not interact with cytochrome P450 enzymes or drug transporters and has minimal potential for metabolic drug-drug interactions [12, 16]. However, its pharmacodynamic effects on intestinal absorption produce several clinically important interaction considerations:

Increased oral medication absorption. By increasing intestinal absorptive surface area, enhancing mucosal barrier function, and slowing gastric emptying, teduglutide may increase the rate and extent of absorption of concomitantly administered oral medications. This effect is particularly relevant for medications with a narrow therapeutic index. The prescribing information recommends monitoring of concomitant oral medications that require dose titration or have a narrow therapeutic index, as dose adjustments of such medications may be required during and after teduglutide treatment [12].

Oral anticoagulants. Patients receiving oral anticoagulants (warfarin, acenocoumarol) should have increased monitoring of International Normalized Ratio (INR) during initiation and discontinuation of teduglutide, as changes in intestinal absorptive function may alter anticoagulant bioavailability and dose-response [12].

Thyroid hormone replacement. Patients with SBS-IF frequently require thyroid hormone supplementation; changes in levothyroxine absorption during teduglutide treatment may necessitate dose adjustment guided by thyroid function testing.

Immunosuppressants. SBS-IF patients with underlying Crohn's disease may be receiving concomitant immunosuppressive therapy (azathioprine, 6-mercaptopurine, methotrexate, corticosteroids, biologic agents). No specific pharmacokinetic interactions with teduglutide have been characterized, but the potential for altered oral immunosuppressant absorption should be considered.

Fluid and electrolyte management. The primary therapeutic effect of teduglutide (increased intestinal fluid absorption) requires coordinated reduction of parenteral support to avoid fluid overload. Parenteral support volumes should be re-

duced gradually under clinical supervision as intestinal absorptive function improves, with monitoring of fluid status, electrolytes, and renal function [12, 14].

Octreotide and somatostatin analogs. Octreotide and lanreotide suppress endogenous GLP-2 secretion and may attenuate the intestinotrophic response to teduglutide through indirect mechanisms, though direct receptor antagonism does not occur. Concurrent use is not specifically contraindicated but may reduce efficacy [47].

Loperamide and antimotility agents. Commonly co-administered in SBS to reduce intestinal transit and increase absorption time. No pharmacological interaction with teduglutide; the combination is synergistic in concept (slowed transit plus increased absorptive capacity).

Cholestyramine and bile acid sequestrants. Commonly used in SBS-IF patients with intact colon to manage bile acid-induced diarrhea. No interaction with teduglutide; both address distinct pathophysiological contributors to malabsorption.

Proton pump inhibitors and H2 receptor antagonists. GLP-2R activation reduces gastric acid secretion. Concurrent acid suppression is common in SBS-IF patients and does not require adjustment.

11. Adverse Events and Safety Signal

11.1 Common adverse events

The principal adverse events at the approved dose (0.05 mg/kg/day subcutaneously) in adult clinical trials are [6, 12]:

- Abdominal pain (28 percent teduglutide versus 23 percent placebo in STEPS)
- Nausea (26 percent versus 14 percent placebo)
- Injection site reactions (26 percent; erythema, pain, swelling at the injection site)
- Abdominal distension (17 percent versus 2 percent placebo)
- Stoma complications in patients with stomas (16 percent; stomal swelling, increased stomal output, peristomal skin irritation)
- Headache (16 percent versus 12 percent placebo)
- Vomiting (14 percent)
- Fluid overload (12 percent; peripheral edema, weight gain from increased intestinal fluid absorption)

Most adverse events are mild to moderate in severity, occur principally in the first weeks of treatment, and are consistent with the pharmacological mechanism (intestinal trophic stimulation and increased absorptive function). The stoma complications and fluid overload reflect the intended therapeutic effect and are managed by appropriate parenteral support adjustment.

In pediatric patients, the most common adverse events were vomiting (51.7 percent), pyrexia (43.8 percent), upper respiratory tract infection (41.6 percent), cough (33.7 percent), and abdominal pain (treatment-related in 5.6 percent) [21, 44].

11.2 Colorectal polyps and neoplasia risk

The most clinically significant class-specific safety concern is the formation of intestinal polyps, identified in both preclinical carcinogenicity studies and in clinical trials [11, 13]. In the pooled STEPS trial series, colon polyps were present at baseline colonoscopy in approximately 12 percent of patients and were detected post-treat-

ment in approximately 18 percent of patients, including in individuals without baseline polyps [11]. Postmarketing reports have documented colorectal, gastric, and small intestinal (duodenal, ileal, and jejunal) polyps during teduglutide treatment. The majority have been hyperplastic or benign adenomatous polyps; no cases of colorectal carcinoma definitively attributable to teduglutide have been reported in clinical trials or postmarketing surveillance [46].

The Gattex prescribing information and REMS program mandate the following colonoscopy surveillance schedule [11, 12]:

- Colonoscopy within 6 months before initiating teduglutide. Remove any polyps detected before starting treatment.
- Follow-up colonoscopy after 1 year of treatment (or sooner if clinically indicated).
- Subsequent colonoscopy every 5 years during continued treatment.
- Discontinue teduglutide if intestinal malignancy is diagnosed.

11.3 Intestinal obstruction

Intestinal obstruction has been reported in clinical trials and postmarketing settings [12]. The mechanism may involve intestinal mucosal hypertrophy in segments with pre-existing stricture or narrowing (common in Crohn's disease and in post-surgical adhesive disease). Patients should be monitored for signs of intestinal obstruction, and teduglutide should be temporarily discontinued in the setting of confirmed obstruction.

11.4 Biliary and pancreatic disease

Cholecystitis, cholangitis, and cholelithiasis have been reported at rates modestly exceeding placebo in clinical trials [12]. The GLP-2 receptor is expressed in the biliary epithelium and the pancreas, and trophic stimulation of these tissues is a plausible mechanism. Pancreatitis has been reported in rare cases. Patients should be monitored for symptoms of biliary and pancreatic disease.

11.5 Fluid overload

Increased intestinal fluid absorption during teduglutide treatment can produce fluid overload if parenteral support volumes are not reduced in parallel. Clinical manifestations include peripheral edema, weight gain, dyspnea, and heart failure exacerbation. Careful, gradual reduction of parenteral support under clinical supervision is essential [12, 14].

11.6 Immunogenicity

Anti-teduglutide antibodies have been detected in approximately 3 percent of adult patients and up to 18 percent of pediatric patients in clinical trials [12, 21]. The antibodies were generally low-titer and non-neutralizing, and no correlation between antibody development and loss of clinical efficacy or adverse events was identified.

11.7 Pregnancy and lactation

Animal reproduction studies in rats and rabbits at doses up to 50 times the human dose did not reveal evidence of teratogenicity or adverse developmental effects [12]. Human pregnancy data are limited. The compound is classified as pregnancy category B (no adequate human studies; animal studies show no risk). Lactation data are limited; use during pregnancy and lactation should be guided by clinical judgment regarding benefit-risk.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative intestinotrophic agents or GLP-2 receptor agonists against teduglutide, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to represent the principal therapeutic alternatives and developmental candidates in the SBS-IF treatment landscape, with priority on compounds that have produced clinical evidence or that are in active clinical development.

12.1 Glepaglutide (ZP1848)

Mechanism: Long-acting GLP-2 analog containing 9 amino acid substitutions relative to native GLP-2 and a C-terminal extension of 6 lysine residues, yielding a plasma half-life of approximately 50 hours and enabling once-weekly or twice-weekly subcutaneous dosing [48]. Glepaglutide retains full agonist activity at the GLP-2R.

Development trajectory: Zealand Pharma advanced glepaglutide through Phase 3 clinical development. The Phase 3 EASE SBS 1 trial (106 patients randomized) demonstrated that glepaglutide twice weekly significantly reduced weekly parenteral support volumes from baseline to week 24 versus placebo (mean change: minus 5.13 versus minus 2.85 L/week; $P = 0.0039$) [48]. Nine glepaglutide-treated patients achieved complete enteral autonomy versus none on placebo. The once-weekly dosing arm showed a numerically smaller but clinically meaningful reduction (minus 3.13 L/week). Ninety-six of 102 completing patients enrolled in the EASE SBS 2 long-term extension.

In December 2024, the FDA issued a Complete Response Letter for the glepaglutide New Drug Application, citing insufficient evidence to establish efficacy and safety at the proposed marketed dose [49]. Zealand Pharma indicated plans for European Marketing Authorization Application submission and additional clinical data generation.

Novelty: Moderate. The GLP-2R agonist mechanism is shared with teduglutide. The novelty is in the extended half-life enabling less frequent dosing.

Effect size: The EASE SBS 1 primary endpoint effect (minus 5.13 L/week reduction, twice weekly) is numerically comparable to the STEPS teduglutide data, though cross-trial comparisons are limited by differences in patient populations and baseline parenteral support volumes.

Promising potential: Moderate. Positive Phase 3 data but the FDA CRL represents a regulatory setback. European regulatory submission is anticipated. If approved, the less frequent dosing schedule would be a meaningful practical advantage over daily teduglutide.

Side-effect profile: Common adverse events include injection site reactions, abdominal pain, nausea, and vomiting, similar to teduglutide. The class-specific risks (polyp formation, neoplastic concern, biliary disease) are expected to be comparable given the shared mechanism.

Overall validation: Moderate. Positive Phase 3 data with regulatory challenges.

Comparison to teduglutide: Glepaglutide's primary advantage is dosing convenience (twice weekly or once weekly versus daily). Teduglutide has the advantages of established regulatory approval, more than a decade of clinical and postmarketing safety experience, and an established prescribing and monitoring infrastructure.

12.2 Apraglutide (FE 203799)

Mechanism: Long-acting GLP-2 analog designed for once-weekly subcutaneous dosing through amino acid substitutions at positions 8, 11, 16, and 30 of GLP-2 that confer enhanced stability and prolonged pharmacokinetics [50]. The rat intravenous elimination half-life of apraglutide is approximately 159 minutes versus 19 minutes for teduglutide.

Development trajectory: Developed by VectivBio AG (Basel, Switzerland), now part of Ironwood Pharmaceuticals. Phase 2 studies demonstrated significant increases in intestinal fluid and energy absorption in SBS-IF patients [51]. The STARS Phase 3 trial, described as the largest Phase 3 trial conducted in SBS-IF, reported

positive topline results in February 2024, with apraglutide demonstrating significant reduction in parenteral support requirements versus placebo [52]. Ironwood Pharmaceuticals announced plans for U.S. regulatory submission in early 2025.

Novelty: Moderate. Same GLP-2R agonist mechanism; novelty lies in the optimized peptide engineering for once-weekly dosing.

Effect size: Phase 3 topline results indicate significant separation from placebo on the primary endpoint. Cross-trial comparison with teduglutide STEPS data is not directly interpretable, though the effect appears broadly comparable.

Promising potential: Moderate to high. Positive Phase 3 results and anticipated regulatory submission. If approved, once-weekly dosing would represent a substantial improvement in treatment burden.

Side-effect profile: Phase 3 safety data indicate high treatment compliance, low incidence of injection site reactions, and acceptable gastrointestinal tolerability [52]. Long-term safety data including colorectal polyp incidence are not yet available at the depth of the teduglutide postmarketing database.

Overall validation: Moderate. Positive Phase 3 data, regulatory submission anticipated, but not yet approved.

Comparison to teduglutide: Apraglutide's primary advantage is the once-weekly dosing schedule. Teduglutide retains the advantages of established approval, long-term safety data, and clinical familiarity. Apraglutide represents the most convenient dosing option among the GLP-2R agonists if approved.

12.3 Native GLP-2 (human GLP-2[1-33])

Mechanism: The endogenous 33-amino-acid proglucagon-derived hormone released from intestinal L-cells in response to luminal nutrients. Full agonist at the GLP-2R with identical receptor-binding pharmacology to teduglutide but an in vivo half-life of approximately 7 minutes due to rapid DPP-IV cleavage [1, 2].

Development trajectory: Native GLP-2 was evaluated in early clinical studies by Jeppesen et al. (2001), demonstrating improved intestinal absorption in SBS patients with no colon during continuous subcutaneous administration [43]. The impractical pharmacokinetic profile (multiple daily injections or continuous infusion

required) precluded clinical development. The compound served as proof-of-concept validation for the GLP-2R agonist mechanism and as the foundation for DPP-IV-resistant analog development.

Novelty: Low. Native GLP-2 is the endogenous ligand and reference standard for the class.

Effect size: Demonstrated increases in intestinal absorption in SBS patients, but the effect was limited by the impractical pharmacokinetic profile.

Promising potential: Low as a therapeutic agent. Remains a valuable research tool for fundamental GLP-2 biology.

Side-effect profile: Well tolerated in short-term studies; the endogenous nature of the peptide minimizes immunogenicity concerns [43].

Overall validation: High for physiological understanding; not applicable for therapeutic development.

Comparison to teduglutide: Native GLP-2 and teduglutide are pharmacologically identical at the receptor level. The sole clinically relevant difference is metabolic stability (7 minutes versus 2 to 3 hours). For research applications requiring GLP-2R activation in cell-based assays, native GLP-2 is equally effective. For in vivo studies or therapeutic applications, teduglutide is required owing to the half-life requirement.

12.4 Growth hormone with glutamine (somatropin plus L-glutamine)

Mechanism: Recombinant human growth hormone (somatropin, Zorbtive) combined with oral glutamine supplementation and a modified diet represents an alternative intestinotrophic strategy operating through systemic IGF-1 elevation, protein anabolism, and direct effects on intestinal adaptation [53, 54]. Zorbtive was FDA-approved in 2003 for short bowel syndrome, making it the first approved intestinotrophic therapy before teduglutide.

Development trajectory: The Byrne et al. (1995, 2005) studies established that recombinant growth hormone at 0.1 mg/kg/day subcutaneously for 4 weeks combined with oral glutamine and dietary modification produced reductions in par-

enteral nutrition volume in a subset of SBS patients [53, 54]. Effect was modest and not universally replicated; some controlled trials showed no benefit of growth hormone over diet modification alone [55].

Novelty: Low. Growth hormone physiology and glutamine metabolism are well characterized. The combination is a nutritional-pharmacological approach rather than a targeted receptor agonist strategy.

Effect size: Modest and inconsistent across controlled trials. Effect sizes appear smaller and less reproducible than teduglutide in cross-trial comparison. The short treatment duration (4 weeks) and the absence of sustained long-term data limit interpretation [54, 55].

Promising potential: Low. Zorbtive remains available but is infrequently used for SBS-IF in the post-teduglutide era.

Side-effect profile: Growth hormone therapy produces dose-dependent fluid retention, arthralgias, carpal tunnel syndrome, hyperglycemia, and theoretical promotion of neoplasia through systemic IGF-1 elevation [54]. The adverse-event burden at therapeutic doses is substantially greater than teduglutide.

Overall validation: Low to moderate. FDA-approved (2003) with limited clinical evidence and limited clinical adoption.

Comparison to teduglutide: Teduglutide produces larger, more consistent, and more sustained reductions in parenteral nutrition requirements with a more favorable adverse-event profile. Growth hormone combination therapy represents a historical alternative that has been largely supplanted by teduglutide.

12.5 Somatropin (recombinant human growth hormone, monotherapy)

Mechanism: Somatropin monotherapy (without glutamine supplementation) stimulates intestinal adaptation through systemic IGF-1 elevation and protein anabolic effects. The mechanism partially overlaps with the downstream IGF-1 pathway activated by GLP-2R agonism but lacks the localized intestinal specificity of teduglutide.

Development trajectory: Somatropin has been used off-label as monotherapy for intestinal rehabilitation in SBS-IF, outside the approved Zorbtive combination indication. The Seguy et al. (2003) study evaluated low-dose growth hormone in home parenteral nutrition-dependent SBS patients and reported modest improvements in intestinal absorption [56]. Published studies are heterogeneous in design, dose, duration, and endpoints.

Novelty: Low. Growth hormone physiology is extensively characterized.

Effect size: Variable and generally modest. Some studies report transient improvements in intestinal absorption during treatment, with loss of benefit after discontinuation. The effect is not sustained in the manner demonstrated by teduglutide in long-term extension studies [56].

Promising potential: Low. Somatropin monotherapy for SBS-IF is not a focus of active clinical development, and its use has declined with the availability of teduglutide.

Side-effect profile: Similar to the growth hormone plus glutamine combination: fluid retention, arthralgias, hyperglycemia, and the systemic effects of supraphysiological IGF-1 elevation. The risk-benefit profile is less favorable than teduglutide.

Overall validation: Low. Limited clinical evidence for monotherapy in SBS-IF, off-label use.

Comparison to teduglutide: Teduglutide is superior in mechanism specificity, clinical evidence quality and quantity, regulatory validation, and long-term efficacy. Somatropin monotherapy does not represent a clinically competitive alternative.

12.6 Comparator summary

The five comparators span the SBS-IF treatment landscape. **Glepaglutide** and **apraglutide** represent next-generation GLP-2R agonists with extended half-lives enabling less frequent dosing; both have produced positive Phase 3 data but neither has achieved regulatory approval (glepaglutide received an FDA CRL in December 2024; apraglutide regulatory submission was anticipated in early 2025). **Native GLP-2** is the endogenous ligand and proof-of-concept compound that established the GLP-2R agonist mechanism but is pharmacokinetically impractical for clinical use.

Growth hormone with glutamine and somatropin monotherapy represent earlier-generation, mechanistically less specific approaches with modest and inconsistent clinical evidence that have been largely supplanted by teduglutide.

Teduglutide occupies the position of established standard of care for pharmacological management of SBS-IF. It is the only GLP-2R agonist with regulatory approval in both the United States and the European Union, the only GLP-2R agonist with more than a decade of clinical and postmarketing safety experience, and the only compound in this class with both adult and pediatric approved indications. The principal limitation is the requirement for daily subcutaneous injection, which the next-generation long-acting analogs (glepaglutide, apraglutide) are designed to address.

The clinical landscape for SBS-IF is evolving. If glepaglutide or apraglutide achieve regulatory approval, the treatment decision will shift from a choice of mechanism to a choice of dosing convenience, and the comparative long-term safety and efficacy data between the GLP-2R agonists will become the determinant of clinical selection. For the present, teduglutide remains the only approved GLP-2R agonist and the reference standard against which all other SBS-IF pharmacotherapies are measured.

13. References

1. Drucker DJ, Shi Q, Crivici A, et al. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. *Nat Biotechnol.* 1997;15(7):673-677.
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. Rowland KJ, Brubaker PL. The "cryptic" mechanism of action of glucagon-like peptide-2. *Am J Physiol Gastrointest Liver Physiol.* 2011;301(1):G1-G8.
4. Yusta B, Holland D, Koehler JA, et al. ErbB signaling is required for the proliferative actions of GLP-2 in the murine gut. *Gastroenterology.* 2009;137(3):986-996.
5. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu Rev Physiol.* 2014;76:561-583.
6. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology.* 2012;143(6):1473-1481.
7. Schwartz LK, O'Keefe SJD, Fujioka K, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. *Clin Transl Gastroenterol.* 2016;7(2):e142.
8. Iyer KR, Kunecki M, Boullata JI, et al. Independence from parenteral nutrition and intravenous fluid support during treatment with teduglutide among patients with intestinal failure associated with short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2017;41(6):946-951.
9. NPS Pharmaceuticals. FDA approves Gattex (teduglutide [rDNA origin]) for injection for the treatment of adult short bowel syndrome. Press release, December 21, 2012.
10. Takeda Pharmaceutical Company. U.S. FDA approves Gattex (teduglutide) for children 1 year of age and older with short bowel syndrome (SBS). Press release, May 17, 2019.

11. Compher C, Gilroy R, Pertkiewicz M, et al. Colon polyps in patients with short bowel syndrome before and after teduglutide: post hoc analysis of the STEPS study series. *Clin Nutr.* 2020;39(7):2136-2141.
12. Gattex (teduglutide) for injection, for subcutaneous use. Full prescribing information. Takeda Pharmaceuticals U.S.A., Inc. Revised 2024.
13. Drucker DJ. The discovery of GLP-2 and development of teduglutide for short bowel syndrome. *ACS Pharmacol Transl Sci.* 2020;3(1):3-15.
14. Pironi L, Arends J, Bozzetti F, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr.* 2016;35(2):247-307.
15. Marier JF, Beliveau M, Bhutta ZA, et al. Pharmacokinetics, safety, and tolerability of teduglutide, a glucagon-like peptide-2 (GLP-2) analog, following multiple ascending subcutaneous administrations in healthy subjects. *J Clin Pharmacol.* 2008;48(11):1289-1299.
16. Marier JF, Mouksassi MS, Sahota S, et al. Population pharmacokinetics of teduglutide following repeated subcutaneous administrations in healthy participants and in patients with short bowel syndrome and Crohn's disease. *J Clin Pharmacol.* 2010;50(4):466-476.
17. Drucker DJ, Erlich P, Asa SL, Bhatt RS. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci U S A.* 1996;93(15):7911-7916.
18. 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.
19. Tsai CH, Hill M, Asa SL, Brubaker PL, Drucker DJ. Intestinal growth-promoting properties of glucagon-like peptide-2 in mice. *Am J Physiol.* 1997;273(1 Pt 1):E77-E84.
20. Jeppesen PB, Sanguinetti EL, Buchman A, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut.* 2005;54(9):1224-1231.
21. Kocoshis SA, Merritt RJ, Hill S, et al. Safety and efficacy of teduglutide in pediatric patients with intestinal failure due to short bowel syndrome: a 24-week, Phase III study. *JPEN J Parenter Enteral Nutr.* 2020;44(4):621-631.

22. Yusta B, Huang L, Munroe D, et al. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. *Gastroenterology*. 2000;119(3):744-755.
23. Leen JLS, Izzo A, Uber R, Drucker DJ. Mechanism of action of glucagon-like peptide-2 to increase IGF-I mRNA in intestinal subepithelial fibroblasts. *Endocrinology*. 2011;152(2):436-446.
24. Dube PE, Forse CL, Bahrami J, Brubaker PL. The essential role of insulin-like growth factor-1 in the intestinal tropic effects of glucagon-like peptide-2 in mice. *Gastroenterology*. 2006;131(2):589-605.
25. Dube PE, Rowland KJ, et al. GLP-2, EGF, and the intestinal epithelial IGF-1 receptor interactions in the regulation of crypt cell proliferation. *Endocrinology*. 2020;161(4):bqaa040.
26. Yusta B, Holland D, Koehler JA, et al. ErbB signaling is required for the proliferative actions of GLP-2 in the murine gut. *Gastroenterology*. 2009;137(3):986-996.
27. Orskov C, Hartmann B, Poulsen SS, et al. GLP-2 stimulates colonic growth via KGF, released by subepithelial myofibroblasts with GLP-2 receptors. *Regul Pept*. 2005;124(1-3):105-112.
28. Benjamin MA, McKay DM, Yang PC, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. *Gut*. 2000;47(1):112-119.
29. Nagell CF, Wettergren A, Pedersen JF, Mortensen D, Holst JJ. Glucagon-like peptide-2 inhibits antral emptying in man, but is not as potent as glucagon-like peptide-1. *Scand J Gastroenterol*. 2004;39(4):353-358.
30. Guan X, Stoll B, Lu X, et al. GLP-2-mediated up-regulation of intestinal blood flow and glucose uptake is nitric oxide-dependent in TPN-fed piglets. *Gastroenterology*. 2003;125(1):136-147.
31. Cheeseman CI. Upregulation of SGLT-1 transport activity in rat jejunum induced by GLP-2 infusion in vivo. *Am J Physiol*. 1997;273(6):R1965-R1971.
32. Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2004;286(6):G964-G972.

33. Jeppesen PB, Sanguinetti EL, Buchman AL, et al. Enteral autonomy and days off parenteral support with teduglutide treatment for short bowel syndrome in the STEPS trials. *JPEN J Parenter Enteral Nutr.* 2020;44(4):697-706.
34. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clin Nutr.* 2008;27(3):328-339.
35. Scott RB, Kirk D, MacNaughton WK. GLP-2 augments the adaptive response to massive intestinal resection in rat. *Am J Physiol.* 1998;275(5):G911-G921.
36. Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. *Am J Physiol Gastrointest Liver Physiol.* 2004;286(6):G964-G972.
37. Burrin DG, Stoll B, Jiang R, et al. GLP-2 stimulates intestinal growth in premature TPN-fed pigs by suppressing proteolysis and apoptosis. *Am J Physiol Gastrointest Liver Physiol.* 2000;279(6):G1249-G1256.
38. Boushey RP, Yusta B, Drucker DJ. Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. *Am J Physiol.* 1999;277(5):E937-E947.
39. Tavakkolizadeh A, Shen R, Abraham P, et al. Glucagon-like peptide 2 (GLP-2) promotes intestinal recovery following chemotherapy-induced enteritis in the rat. *Dig Dis Sci.* 2000;45(6):1141-1147.
40. Drucker DJ, Yusta B, Boushey RP, DeForest L, Brubaker PL. Human [Gly2]GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. *Am J Physiol.* 1999;276(1):G79-G91.
41. Booth C, Booth D, Williamson S, et al. Teduglutide ([Gly2]GLP-2) protects small intestinal stem cells from radiation damage. *Cell Prolif.* 2004;37(6):385-400.
42. Bremholm L, Hornum M, Henriksen BM, Larsen S, Holst JJ. Glucagon-like peptide-2 increases mesenteric blood flow in humans. *Scand J Gastroenterol.* 2009;44(3):314-319.
43. 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.

44. Carter BA, Cohran VC, Cole CR, et al. Safety findings in pediatric patients during long-term treatment with teduglutide for short-bowel syndrome-associated intestinal failure: pooled analysis of 4 clinical studies. *JPEN J Parenter Enteral Nutr.* 2021;45(4):395-404.
45. Pironi L, Sasdelli AS, Vreugdenhil G, et al. Baseline characteristics of adult patients treated and never treated with teduglutide in a multinational short bowel syndrome and intestinal failure registry. *Nutrients.* 2024;16(15):2513.
46. Joly F, Seguy D, Nuzzo A, et al. Long-term safety analysis of teduglutide treatment in patients with short bowel syndrome-associated intestinal failure. *Transplantation.* 2023;107(Suppl 1):S58.
47. Jeppesen PB. Pharmacologic options for intestinal rehabilitation in patients with short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2014;38(1 Suppl):45S-52S.
48. Naimi RM, Hvistendahl MK, Enevoldsen LH, 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.* 2025;168(2):282-292.
49. Zealand Pharma. U.S. Food and Drug Administration issues Complete Response Letter for the glepaglutide New Drug Application for the treatment of short bowel syndrome. Press release, December 19, 2024.
50. 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.
51. Eliasson J, Hvistendahl MK, Freund N, et al. Apraglutide, a novel glucagon-like peptide-2 analog, improves fluid absorption in patients with short bowel syndrome intestinal failure: findings from a placebo-controlled, randomized phase 2 trial. *JPEN J Parenter Enteral Nutr.* 2022;46(4):896-904.
52. Ironwood Pharmaceuticals. Once-weekly apraglutide showed consistent treatment effect across baseline demographics and disease characteristics in adults with short bowel syndrome with intestinal failure (SBS-IF). Press release, October 2024.

53. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN J Parenter Enteral Nutr. 1995;19(4):296-302.
54. Byrne TA, Wilmore DW, Iyer K, et al. Growth hormone, glutamine, and an optimal diet reduces parenteral nutrition in patients with short bowel syndrome: a prospective, randomized, placebo-controlled, double-blind clinical trial. Ann Surg. 2005;242(5):655-661.
55. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. 2000;47(2):199-205.
56. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology. 2003;124(2):293-302.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Teduglutide is approved by the United States Food and Drug Administration (as Gattex) and by the European Commission (as Revestive) for the treatment of short bowel syndrome with intestinal failure in adult and pediatric patients dependent on parenteral support. Research-grade preparations are available from chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot. Prescribing information, including colonoscopy surveillance requirements and REMS obligations, should be consulted before any clinical or research application.