

RESEARCH MONOGRAPH . COMPOUND PROFILE

Apraglutide

A rationally designed, DPP-IV-resistant, long-acting synthetic analog of human glucagon-like peptide-2 bearing four amino acid substitutions that confer very low systemic clearance and high plasma protein binding, enabling once-weekly subcutaneous dosing for the treatment of short bowel syndrome with intestinal failure and under investigation for steroid-refractory gastrointestinal acute graft-versus-host disease.

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ABSTRACT

Apraglutide (FE 203799) is a synthetic 33-amino-acid peptide analog of human glucagon-like peptide-2 (GLP-2) and a potent, selective, full agonist of the GLP-2 receptor (GLP-2R), developed as a next-generation intestinotrophic agent for the treatment of short bowel syndrome with intestinal failure (SBS-IF) and under investigation for steroid-refractory gastrointestinal acute graft-versus-host disease (GI aGVHD). The compound differs from native human GLP-2(1-33) by four amino acid substitutions ([Gly2, Nle10, D-Phe11, Leu16]hGLP-2(1-33)-NH₂) that confer resistance to dipeptidyl peptidase-IV (DPP-IV) degradation, very low systemic clearance, slow absorption from the subcutaneous depot, and high plasma protein binding, resulting in an elimination half-life of approximately 72 hours in healthy volunteers and enabling once-weekly subcutaneous administration [1, 2]. In head-to-head rat intravenous pharmacokinetic comparisons, apraglutide demonstrated a clearance of 0.27 mL/kg per minute versus 9.9 mL/kg per minute for teduglutide and 2.8 mL/kg per minute for glepaglutide, and an elimination half-life of 159 minutes versus 19 minutes for teduglutide and 16 minutes for glepaglutide [1]. The compound retains potency and selectivity at the human GLP-2 receptor comparable to native GLP-2 and teduglutide, with approximately two-fold greater potency than both in cell-based receptor activation assays [1]. Apraglutide was originally discovered at Ferring Pharmaceuticals (development code FE 203799) and subsequently licensed to GLyPharma Therapeutic in 2012, acquired by Therachon (a Novo Holdings-backed rare disease company), transitioned to VectivBio AG, and acquired by Ironwood Pharmaceuticals in 2023 [3, 4]. The compound received

orphan drug designation from the United States Food and Drug Administration, the European Medicines Agency, and the Japanese regulatory authority for SBS-IF. The pivotal Phase 3 STARS trial (NCT04627025), a global, randomized, double-blind, placebo-controlled study in 164 adults with SBS-IF across 73 centers in 18 countries, met its primary endpoint: apraglutide-treated patients achieved a 25.5 percent relative reduction in weekly parenteral support volume at week 24 versus 12.5 percent for placebo ($P = 0.001$), with treatment effect evident from week 8 [5, 6]. Secondary endpoints demonstrated that 43 percent of apraglutide-treated patients gained at least one additional day off parenteral support per week (versus 27.5 percent for placebo, $P = 0.04$), and 6.4 percent of apraglutide-treated patients achieved complete enteral autonomy at week 24 compared to 0 percent on placebo [5]. Long-term extension data through 48 weeks showed 12.5 percent of apraglutide-treated patients achieving enteral autonomy versus 7.4 percent on placebo, with 27 patients overall achieving enteral autonomy across the development program [7]. In metabolic balance studies, once-weekly apraglutide at 5 mg subcutaneous increased wet weight absorption by 741 g/day, increased energy absorption by 1095 kJ/day, and increased sodium absorption by 38 mmol/day, making apraglutide the first GLP-2 analog to significantly improve energy absorption across the full SBS patient spectrum as measured by bomb calorimetry [8, 9]. The Phase 2 STARGAZE trial in steroid-refractory GI aGVHD demonstrated a 58.1 percent overall response rate at day 28 (versus 38.8 percent in a matched MAGIC control cohort) and a lower cumulative non-relapse mortality at day 180 (33.3 percent versus 41.9 percent) [10]. Adverse events across the clinical program have been predominantly mild to moderate gastrointestinal effects (decreased stoma output, stoma

complications, nausea, flatulence, abdominal pain) consistent with the pharmacological intestinotrophic mechanism, with injection site reactions, polyuria, and edema also reported at low incidence [8, 11]. Ironwood Pharmaceuticals initiated a rolling NDA submission in January 2025; following FDA feedback requiring a confirmatory Phase 3 trial, the STARS-2 study is planned with site initiations in the second quarter of 2026 and an NDA submission target before end of 2029 [7, 12]. This monograph reviews the chemistry and peptide engineering of apraglutide; the GLP-2 receptor pharmacology and downstream intestinotrophic signaling; the comprehensive pharmacokinetic profile in healthy volunteers, SBS patients, and special populations; the preclinical intestinal growth pharmacology; the clinical evidence base across SBS-IF, metabolic balance, and GI aGVHD indications; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety signal; and a comparative assessment of five GLP-2 receptor agonist candidates against apraglutide on five competency standards. The compound is not approved by any regulatory authority as of the monograph revision date.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Apraglutide (proposed INN; WHO recommended INN assigned).

Development codes: FE 203799 (Ferring Pharmaceuticals, the original development code and the identifier used in early pharmacological characterization papers).

Chemical Abstracts Service registry number: 1295353-98-8 (free base peptide).

Structural designation: [Gly2, Nle10, D-Phe11, Leu16]hGLP-2(1-33)-NH₂. The compound is a C-terminally amidated synthetic peptide analog of human glucagon-like peptide-2 bearing four site-specific amino acid substitutions relative to the native 33-residue sequence.

1.2 Structural class and chemistry

Apraglutide is a synthetic peptide belonging to the glucagon superfamily of proglucagon-derived hormones. The parent molecule, human GLP-2(1-33), is a 33-amino-acid peptide produced by post-translational cleavage of proglucagon in enteroendocrine L-cells of the distal ileum and colon. Native GLP-2 has a plasma half-life of approximately 7 minutes owing to rapid N-terminal cleavage by dipeptidyl peptidase-IV (DPP-IV) at the Ala2-Asp3 bond [13].

Molecular formula: C₁₇₂H₂₆₃N₄₃O₅₂ (free base).

Molecular weight: 3,765.20 g/mol (free base).

Amino acid substitutions and their rationale: The four substitutions in apraglutide are each designed to address a specific pharmacokinetic or stability limitation of the native peptide. (1) Gly2: substitution of alanine at position 2 with glycine removes the DPP-IV cleavage site, conferring resistance to the principal endopeptidase responsible for native GLP-2 inactivation. This modification is shared with teduglutide ([Gly2]hGLP-2) and is the minimal pharmacokinetic enhancement in the GLP-2 analog class [1, 13]. (2) Nle10: substitution of methionine at position 10

with norleucine eliminates the thioether side chain susceptible to oxidative degradation, improving chemical stability without altering receptor binding. (3) D-Phe11: substitution of the L-phenylalanine at position 11 with the D-enantiomer introduces a non-natural stereocenter that retards proteolytic cleavage at this segment of the peptide backbone. (4) Leu16: substitution at position 16 with leucine further modifies the peptide backbone conformation and contributes to the high plasma protein binding that is a distinctive pharmacokinetic feature of apraglutide [1, 2].

Physical properties: White to off-white lyophilized powder. Soluble in water, phosphate-buffered saline, and dimethyl sulfoxide. The C-terminal amide (rather than free carboxylic acid) is the synthetic and formulated form.

1.3 Synthesis

Apraglutide is manufactured by solid-phase peptide synthesis (SPPS) using standard Fmoc (fluorenylmethyloxycarbonyl) chemistry on a Rink amide resin to generate the C-terminal amide. The synthesis proceeds through sequential coupling of protected amino acids in the C-to-N direction, with the four non-native residues (Fmoc-Gly-OH at position 2, Fmoc-Nle-OH at position 10, Fmoc-D-Phe-OH at position 11, Fmoc-Leu-OH at position 16) incorporated at their respective positions. Following chain assembly and global deprotection with trifluoroacetic acid scavenger cocktails, the crude peptide is purified by preparative reversed-phase high-performance liquid chromatography (RP-HPLC) and lyophilized. The final product is characterized by analytical RP-HPLC (purity typically greater than 95 percent), mass spectrometry (electrospray ionization or MALDI-TOF confirmation of molecular weight), amino acid analysis, and peptide content determination. The trifluoroacetate (TFA) counterion from HPLC purification may be exchanged to acetate for pharmaceutical formulations to reduce potential immunogenicity of trifluoroacetate salts. Industrial manufacturing follows current good manufacturing practice (cGMP) for peptide active pharmaceutical ingredients.

2. Abstract

Apraglutide (FE 203799; [Gly2, Nle10, D-Phe11, Leu16]hGLP-2(1-33)-NH₂; CAS 1295353-98-8; molecular formula C₁₇₂H₂₆₃N₄₃O₅₂; molecular weight 3,765.20) is a synthetic, long-acting, once-weekly glucagon-like peptide-2 (GLP-2) receptor agonist developed for the treatment of short bowel syndrome with intestinal failure (SBS-IF) and under investigation for steroid-refractory gastrointestinal acute graft-versus-host disease (GI aGVHD). The compound is distinguished from the first-generation GLP-2 analog teduglutide (Gattex/Revestive, the only approved GLP-2 analog for SBS-IF, requiring daily subcutaneous injection) by a substantially longer elimination half-life (approximately 72 hours versus 1.3 to 2 hours for teduglutide), very low systemic clearance, and high plasma protein binding, properties that derive from the rational engineering of four amino acid substitutions relative to native GLP-2 [1, 2, 14].

The intestinotrophic mechanism of apraglutide is mediated through full agonism at the GLP-2 receptor, a class B G protein-coupled receptor expressed on enteric neurons, subepithelial myofibroblasts, and enteroendocrine cells of the gastrointestinal mucosa. GLP-2 receptor activation stimulates adenylyl cyclase, elevates intracellular cyclic adenosine monophosphate, and triggers a downstream cascade of paracrine growth factor release (epidermal growth factor, insulin-like growth factor-1, keratinocyte growth factor) that promotes crypt cell proliferation, villus elongation, increased mucosal surface area, enhanced intestinal blood flow, reduced mucosal permeability, and inhibition of enterocyte apoptosis [15, 16]. The composite effect is an increase in absorptive capacity for fluid, electrolytes, and macronutrients, which is the mechanistic basis for parenteral support reduction in SBS-IF patients.

The pivotal Phase 3 STARS trial met its primary endpoint with a statistically significant reduction in parenteral support volume at 24 weeks. Metabolic balance studies demonstrated significant improvements in wet weight, energy, and electrolyte absorption. The STARGAZE Phase 2 trial in GI aGVHD demonstrated encouraging response rates relative to matched historical controls. The compound has orphan drug designations in the United States, European Union, and Japan for SBS-IF.

It is not approved by any regulatory authority as of this monograph revision. Ironwood Pharmaceuticals is the current sponsor, with a confirmatory Phase 3 trial (STARS-2) planned for initiation in 2026.

3. Discovery and Development History

3.1 Origin

Apraglutide (FE 203799) was discovered at Ferring Pharmaceuticals as part of a structure-activity relationship program to identify long-acting GLP-2 analogs with improved pharmacokinetic properties relative to native GLP-2 and the first-generation analog teduglutide [1]. The design rationale centered on introducing amino acid modifications that would confer DPP-IV resistance (shared with teduglutide via the Gly2 substitution) while simultaneously engineering additional substitutions to achieve very low systemic clearance, high plasma protein binding, and slow subcutaneous absorption, properties not achieved by teduglutide alone. The selection of the [Gly2, Nle10, D-Phe11, Leu16] combination was the outcome of iterative medicinal chemistry optimization of the GLP-2(1-33) scaffold.

3.2 Licensing and corporate development history

Ferring Pharmaceuticals exclusively licensed apraglutide to GLyPharma Therapeutic Inc., a Montreal-based company, in 2012 [3, 4]. Therachon AG, a Novo Holdings-backed rare disease startup, acquired GLyPharma in 2018, obtaining the exclusive development and commercialization rights to apraglutide [3]. Therachon had been focused on rare bone and metabolic diseases; the acquisition of apraglutide expanded the pipeline into gastrointestinal rare diseases. VectivBio AG was formed as a spin-off or successor entity to the apraglutide program from Therachon, with the compound as the lead asset. VectivBio was listed on the Nasdaq stock exchange in 2021 and advanced apraglutide through Phase 1, Phase 2, and the pivotal Phase 3 STARS trial. Ironwood Pharmaceuticals acquired VectivBio in the second quarter of 2023, bringing apraglutide under the same corporate umbrella as linaclotide (Linzess), Ironwood's marketed guanylate cyclase-C agonist for irritable bowel syndrome with constipation and chronic idiopathic constipation [4, 7].

3.3 Regulatory milestones

The FDA granted orphan drug designation for apraglutide for SBS-IF. The European Medicines Agency and the Japanese regulatory authority similarly granted orphan drug designations. The FDA additionally granted orphan drug designation for apraglutide for the prevention of acute graft-versus-host disease in June 2021 [17]. VectivBio announced the first patient dosed in the pivotal Phase 3 STARS trial on February 3, 2021 [18]. Ironwood initiated a rolling NDA submission for apraglutide for SBS-IF in January 2025 [12]. In April 2025, Ironwood disclosed that following discussions with the FDA, a confirmatory Phase 3 trial (STARS-2) would be required to support approval, based in part on pharmacokinetic analysis indicating that the exposure and dose delivered in the STARS trial were lower than planned due to dose preparation and administration factors [7, 12]. Ironwood aligned with the FDA on the STARS-2 design in late 2025, with a planned 24-week global, randomized, double-blind, placebo-controlled study and site initiations beginning in the second quarter of 2026 [7]. The NDA submission timeline is currently projected before the end of 2029.

3.4 Context within the GLP-2 analog class

Apraglutide is the second GLP-2 analog to reach pivotal Phase 3 development for SBS-IF after teduglutide, and the first to enable once-weekly rather than daily subcutaneous dosing. Glepaglutide (Zealand Pharma) is a third GLP-2 analog that has completed a Phase 3 trial for SBS-IF with twice-weekly dosing. The three compounds represent an evolution of the GLP-2 analog pharmacokinetic profile: teduglutide (daily), glepaglutide (twice-weekly), apraglutide (once-weekly) [1, 19].

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 (GPCR) that is the sole known receptor for the endogenous intestinotrophic hormone GLP-2. The receptor is expressed predominantly in the gastrointestinal tract, with the highest density in the jejunum and ileum, and at lower levels in the stomach, colon, and central nervous system (hypothalamus, brainstem) [15, 16, 20]. Importantly, the GLP-2 receptor is not expressed on intestinal epithelial crypt cells themselves; the trophic effects of GLP-2 on the epithelium are mediated indirectly through paracrine signaling from GLP-2R-expressing cells, principally enteric neurons, subepithelial myofibroblasts, and enteroendocrine cells [15, 16].

4.2 Receptor activation and intracellular signaling

Apraglutide binds to and fully activates the GLP-2 receptor with potency and selectivity comparable to native human GLP-2. In cell-based receptor activation assays using heterologous expression systems, apraglutide was approximately two-fold more potent than both native hGLP-2 and teduglutide for activation of the human GLP-2 receptor [1]. The compound is selective for GLP-2R and does not produce significant activation of the related GLP-1 receptor, glucagon receptor, or other class B GPCRs at pharmacologically relevant concentrations, in contrast to glepaglutide, which demonstrates reduced selectivity [1].

Upon ligand binding, the GLP-2 receptor couples principally to the stimulatory G protein (Gs), activating adenylyl cyclase and elevating intracellular cyclic adenosine monophosphate (cAMP) concentrations. The cAMP-protein kinase A (PKA) signaling cascade is the primary intracellular pathway mediating the intestinotrophic effects [15, 16]. Additional signaling cascades activated downstream of GLP-2R include extracellular signal-regulated kinase 1/2 (ERK1/2), phosphoinositide 3-kinase/Akt (PI3K/Akt), and Wnt/beta-catenin pathways, each contributing to crypt cell proliferation, inhibition of apoptosis, and epithelial restitution [16, 21].

4.3 Downstream paracrine mediators

Because the GLP-2 receptor is not expressed on crypt epithelial cells, the proliferative and anti-apoptotic effects of GLP-2R agonists on the intestinal epithelium are mediated through paracrine growth factors released from GLP-2R-expressing cells [15, 16]. The principal downstream mediators characterized in the literature include:

Insulin-like growth factor-1 (IGF-1): GLP-2R activation on subepithelial myofibroblasts stimulates local production and release of IGF-1, which acts on the epithelial IGF-1 receptor to promote crypt cell proliferation and to increase microvillus length [22, 23]. The IGF-1 pathway intersects with the canonical Wnt signaling pathway that governs intestinal stem cell self-renewal and transit-amplifying cell proliferation in the crypt compartment.

Epidermal growth factor (EGF) and ErbB ligands: GLP-2 treatment increases expression of ErbB receptor ligands in the intestinal mucosa. Inhibition of the ErbB family of receptors or knockout of the intestinal epithelial EGF receptor markedly impairs the proliferative response to GLP-2 [22]. EGF and IGF-1 act synergistically to promote intestinal epithelial proliferation.

Keratinocyte growth factor (KGF) and IGF-2: The intestinotrophic actions of GLP-2 on the colon are mediated in part through KGF and IGF-2, whereas small intestinal growth is primarily linked to IGF-1 and ErbB ligands [22].

4.4 Composite intestinotrophic effects

The composite physiological effect of GLP-2R agonism through these paracrine pathways includes: (a) increased crypt cell proliferation and elongation of the crypt-villus axis, resulting in greater mucosal surface area; (b) increased intestinal length, an effect that has been particularly pronounced with apraglutide in preclinical models [24]; (c) enhanced mesenteric and intestinal blood flow; (d) reduced mucosal permeability through strengthening of tight junctions; (e) inhibition of enterocyte apoptosis; and (f) decreased gastric motility and gastric acid secretion [15, 16]. The aggregate result is improved intestinal absorptive capacity for fluid, electrolytes, and macronutrients, which is the therapeutic mechanism for reducing parenteral support dependence in SBS-IF.

4.5 Unique pharmacological features of apraglutide

In preclinical studies, apraglutide demonstrated an unexpected and distinctive ability to increase intestinal length in addition to the expected crypt-villus elongation, a property reported to be more pronounced than with other GLP-2 analogs [24]. Hargrove et al. (2020) reported that apraglutide exhibited site-specific and temporal effects on intestinal growth in mice, with greater intestinotrophic activity than other GLP-2 peptides when administered at less frequent dosing intervals, directly attributable to the prolonged half-life maintaining pharmacodynamically active concentrations between doses [1, 24].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Apraglutide is administered by subcutaneous injection, the only route studied in clinical development. Absorption from the subcutaneous depot is slow and sustained, a pharmacokinetic feature intentionally engineered through the amino acid substitutions that increase lipophilicity and promote local depot formation [1, 2]. In healthy volunteers receiving weekly subcutaneous doses of 1, 5, or 10 mg, the pharmacokinetic profile demonstrated slow absorption with time to peak plasma concentration (T_{max}) substantially longer than that of teduglutide [2, 25]. Subcutaneous bioavailability is estimated at 54 to 74 percent [2].

5.2 Distribution

Apraglutide demonstrates high plasma protein binding relative to native GLP-2 and other GLP-2 analogs, a property that contributes substantially to the low systemic clearance and prolonged half-life [1, 2]. Mean volume of distribution following subcutaneous administration in healthy volunteers was 55.4 to 105.0 liters, consistent with moderate tissue distribution [25]. The high protein binding serves as a circulating reservoir that maintains pharmacologically active free drug concentrations over the dosing interval.

5.3 Metabolism and elimination

Apraglutide is a peptide and is expected to be metabolized by general proteolytic degradation pathways rather than by cytochrome P450 enzymes. The Gly2 substitution confers resistance to DPP-IV, the principal endopeptidase responsible for inactivation of native GLP-2; the D-Phe11 substitution provides additional resistance to other serine proteases [1]. Mean estimated systemic clearance in healthy volunteers was 16.5 to 20.7 L/day [25]. The elimination half-life is approximately 72 hours in

healthy volunteers and approximately 30 hours in patients with SBS, the difference attributable to altered gastrointestinal physiology and potentially reduced protein binding in the patient population [2, 8].

In head-to-head rat intravenous pharmacokinetic comparisons, clearance values for native hGLP-2, teduglutide, glepaglutide, and apraglutide were 25, 9.9, 2.8, and 0.27 mL/kg per minute, respectively, and elimination half-lives were 6.4, 19, 16, and 159 minutes, respectively [1]. The approximately 37-fold lower clearance and 8-fold longer half-life of apraglutide relative to teduglutide in this preclinical model is consistent with the human pharmacokinetic advantage that enables once-weekly dosing.

5.4 Dose linearity and accumulation

In the Phase 1 healthy volunteer study, weekly subcutaneous administration of apraglutide for 6 weeks demonstrated a linear pharmacokinetic profile with no accumulation after repeated doses at the 1, 5, and 10 mg dose levels [25]. This finding is consistent with the half-life of approximately 72 hours (3 days) relative to the 7-day dosing interval, which allows near-complete washout between doses.

5.5 Pharmacodynamic biomarker

Plasma citrulline, a biomarker of functional enterocyte mass, was used as the principal pharmacodynamic marker in the Phase 1 healthy volunteer study. A dose-dependent increase in plasma citrulline concentration was observed, with the 5 mg and 10 mg doses producing higher citrulline elevations than the 1 mg dose or placebo [25]. The weekly 5 mg dose induced the maximal citrulline response, and increased plasma citrulline levels were sustained for 10 to 17 days after the final administration, indicating a pharmacodynamic effect duration that outlasts the pharmacokinetic half-life and is consistent with the structural intestinal remodeling (villus growth) produced by sustained GLP-2R agonism [25].

5.6 Special populations

Pharmacokinetic studies in individuals with impaired renal function (Phase 1, open-label) demonstrated that a single dose of apraglutide was well tolerated across normal, mild, moderate, and severe renal impairment groups, with pharmacokinetic parameters not requiring dose adjustment [26]. A separate Phase 1 study in in-

dividuals with hepatic impairment similarly evaluated single-dose pharmacokinetics and tolerability [27]. These special population studies support the anticipated registration package and inform dose selection across the SBS-IF population, which frequently includes patients with co-morbid renal or hepatic dysfunction.

5.7 Routes of administration

The only route studied in clinical development is subcutaneous injection. The compound is formulated as a solution for subcutaneous injection in prefilled devices. Clinical doses evaluated include 1 mg, 2.5 mg, 5 mg, and 10 mg administered once weekly. The 5 mg once-weekly dose was selected for pivotal Phase 3 development based on the Phase 1 pharmacodynamic data showing maximal citrulline response at this dose and the Phase 2 metabolic balance data confirming clinically meaningful absorption improvements [8, 9, 25].

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Hargrove et al. (2020) published the comprehensive preclinical pharmacological characterization of apraglutide in the Journal of Pharmacology and Experimental Therapeutics [1]. In cell-based assays of GLP-2 receptor activation using heterologous expression of the human GLP-2R, apraglutide was approximately two-fold more potent than native hGLP-2 and teduglutide, while glepaglutide was less potent and less selective [1]. Apraglutide and teduglutide retained selectivity at the GLP-2 receptor comparable to native hGLP-2, with no significant cross-reactivity at the GLP-1 receptor, glucagon receptor, or other members of the class B GPCR family at pharmacologically relevant concentrations [1].

6.2 In vivo intestinotrophic effects

In mouse intestinal growth studies, apraglutide demonstrated greater intestinotrophic activity than other GLP-2 peptides when administered at less frequent dosing intervals, directly attributable to the prolonged half-life maintaining pharmacodynamically active concentrations [1]. The intestinotrophic response included both the expected crypt-villus elongation and an unexpected marked increase in intestinal length [24].

Connor et al. (2020) published a detailed characterization of site-specific and temporal effects of apraglutide on intestinal growth in mice in the American Journal of Physiology-Gastrointestinal and Liver Physiology [24]. The study demonstrated that apraglutide produced time- and location-dependent intestinotrophic actions, with effects on crypt depth, villus height, and intestinal length that varied by intestinal segment and duration of treatment. The capacity to increase intestinal length, in addition to mucosal surface area, is a potentially clinically meaningful differentiating feature, as increased absorptive length compounds with increased absorptive surface area per unit length to amplify the total absorptive capacity.

6.3 Pharmacokinetic comparisons

The Hargrove et al. (2020) study provided the definitive head-to-head pharmacokinetic comparison across the GLP-2 analog class [1]. In rat intravenous pharmacokinetic studies, the rank order of clearance was native hGLP-2 (25 mL/kg per minute) > teduglutide (9.9) > glepaglutide (2.8) > apraglutide (0.27), and the rank order of half-life was apraglutide (159 minutes) > teduglutide (19) > glepaglutide (16) > native hGLP-2 (6.4). The 93-fold reduction in clearance and 25-fold increase in half-life of apraglutide relative to native GLP-2, and the corresponding 37-fold reduction in clearance and 8-fold increase in half-life relative to teduglutide, established the pharmacokinetic basis for once-weekly dosing [1].

6.4 GvHD preclinical models

VectivBio presented preclinical data supporting apraglutide for the treatment of acute graft-versus-host disease at the 48th Annual Meeting of the European Society for Blood and Marrow Transplantation [28]. The GLP-2 receptor agonist mechanism provides a rationale for GI aGVHD treatment through promotion of intestinal epithelial repair, restoration of mucosal barrier integrity, and reduction of bacterial translocation that drives the inflammatory cascade in GI aGVHD.

7. Clinical Evidence Base

7.1 Phase 1 healthy volunteer pharmacokinetic and pharmacodynamic study

Bolognani et al. (2023) published the characterization of the pharmacokinetic and pharmacodynamic profile of apraglutide in 24 healthy volunteers randomized to placebo or apraglutide at 1 mg, 5 mg, or 10 mg subcutaneous once weekly for 6 weeks [25]. The study demonstrated linear pharmacokinetics with no accumulation, dose-dependent increases in plasma citrulline (the enterocyte mass biomarker), and tolerability across the dose range. The 5 mg dose produced the maximal citrulline response, and citrulline elevations persisted for 10 to 17 days after the last dose, providing pharmacodynamic evidence of sustained intestinal epithelial growth [25].

7.2 Phase 2 randomized placebo-controlled metabolic balance trial (SBS-IF)

Eliasson et al. (2022) published the results of a double-blind, placebo-controlled, randomized, crossover Phase 2 trial in 8 adults with SBS-IF at Copenhagen University Hospital Rigshospitalet [11]. Patients received apraglutide 5 mg and 10 mg subcutaneous once weekly and placebo in a crossover design. Both the 5 mg and 10 mg doses significantly increased urine volume (714 mL/day and 795 mL/day versus placebo, respectively), indicating improved fluid absorption. The 10 mg dose significantly increased urinary sodium excretion by 88 mmol/day and reduced spontaneous fluid intake by 363 mL/day [11]. Adverse events were mild to moderate, including polyuria, decreased stoma output, stoma complications, and edema. Three patients developed anti-apraglutide antibodies without clinical consequences [11].

7.3 Phase 1/2 open-label metabolic balance trial

Eliasson et al. (2022) published a separate open-label Phase 1 and 2 metabolic balance trial in 8 patients with SBS (4 SBS-II, 4 SBS-IF) receiving apraglutide 5 mg once weekly for 4 weeks at Copenhagen University Hospital Rigshospitalet [8]. The meta-

bolic balance methodology, the gold standard for quantifying intestinal absorption, demonstrated statistically significant improvements in multiple absorption parameters:

Wet weight absorption increased by 741 g/day ($P = 0.015$). Fecal output decreased by 680 g/day ($P = 0.018$). Urine production increased by 560 g/day ($P = 0.030$). Energy absorption increased by 1095 kJ/day ($P = 0.024$), with carbohydrate absorption improving by 518 kJ/day ($P = 0.019$) and lipid absorption by 376 kJ/day ($P = 0.026$). Sodium absorption increased by 38 mmol/day ($P = 0.039$) and potassium absorption by 18 mmol/day ($P = 0.020$) [8].

Body weight increased by 1.8 kg ($P = 0.016$), lean body mass increased by 1.7 kg ($P = 0.003$), and fat mass decreased by 1.1 kg ($P = 0.044$), indicating that the weight gain was predominantly lean tissue consistent with intestinal mucosal growth and hydration improvement [8]. Apraglutide is the first GLP-2 analog to demonstrate statistically significant improvement in energy absorption across the full SBS patient spectrum (both stoma and colon-in-continuity patients) as measured by bomb calorimetry, the most rigorous laboratory method for quantifying intestinal energy absorption [8, 9].

7.4 Phase 3 STARS trial (SBS-IF)

The STARS trial (NCT04627025) is the pivotal Phase 3 study of apraglutide in SBS-IF. The trial was a global, randomized, double-blind, placebo-controlled study conducted across 73 centers in 18 countries, enrolling 164 adults with SBS-IF who were dependent on parenteral support. Patients were randomized 2:1 to once-weekly subcutaneous apraglutide 5 mg or placebo for 24 weeks, with a 24-week open-label extension to 48 weeks [5, 6].

Primary endpoint: The primary endpoint was the relative change from baseline in actual weekly parenteral support volume at week 24. Apraglutide-treated patients achieved a 25.5 percent relative reduction versus 12.5 percent for placebo ($P = 0.001$), meeting the primary endpoint with statistical significance [5, 6].

Subgroup analyses: In the stoma subgroup (80 patients), the reduction was more pronounced: 25.6 percent versus 7.8 percent for placebo ($P < 0.001$). In the colon-in-continuity subgroup (83 patients), the numerical benefit did not reach statistical significance: 25.2 percent versus 17.6 percent for placebo ($P = 0.179$) [5, 6].

Secondary endpoints: A significantly higher proportion of apraglutide-treated patients achieved at least one additional day off parenteral support per week at week 24: 43 percent versus 27.5 percent for placebo ($P = 0.04$). Complete enteral autonomy (independence from parenteral support) was achieved by 6.4 percent of apraglutide-treated patients versus 0 percent on placebo at week 24 [5]. At week 48, enteral autonomy rates were 12.5 percent for apraglutide versus 7.4 percent for placebo. Across the full development program, 27 apraglutide-dosed patients achieved enteral autonomy [7].

Treatment effect onset: The treatment effect was observable from week 8, consistent with the time required for GLP-2R-mediated intestinal structural remodeling to translate into measurably improved absorption [5].

Safety: Apraglutide was well tolerated, with treatment compliance exceeding 98 percent. The overall incidence of adverse events was similar between treatment arms. The discontinuation rate due to adverse events was low: 3.6 percent in the apraglutide arm versus 1.9 percent in the placebo arm. Gastrointestinal tolerability adverse events were of low incidence and similar between groups [5, 6].

7.5 Pharmacokinetic findings from the STARS trial

Ironwood disclosed in April 2025 that pharmacokinetic analysis from the STARS trial indicated that the actual drug exposure and dose delivered were lower than planned, attributed to dose preparation and administration factors [7, 12]. This finding contributed to the FDA's request for a confirmatory Phase 3 trial (STARS-2), which will address the dosing methodology to ensure the intended exposure is achieved. Notably, the STARS trial achieved its primary endpoint despite this sub-optimal exposure, suggesting that the true treatment effect at intended exposure levels may be larger than observed.

7.6 Phase 2 STARGAZE trial (GI aGVHD)

The Phase 2 STARGAZE trial evaluated apraglutide in combination with best available therapy (principally ruxolitinib) in patients with steroid-refractory lower-GI acute graft-versus-host disease [10]. The trial enrolled 31 patients and compared outcomes to a matched MAGIC consortium control cohort.

The overall response rate at day 28 was 58.1 percent for STARGAZE patients versus 38.8 percent for MAGIC controls. Durable response at day 56 was 45.1 percent versus 32.2 percent, and the response difference widened further at day 91 (45.1 percent versus 25.8 percent). Complete response reached 29.0 percent at both days 56 and 91. The cumulative incidence of non-relapse mortality at day 180 was lower in STARGAZE (33.3 percent, 95 percent CI 17.5 to 50.1) versus MAGIC controls (41.9 percent, 95 percent CI 24.7 to 58.3) [10]. Apraglutide was well tolerated when added to ruxolitinib in the second-line setting. The mechanistic rationale for GLP-2R agonism in GI aGVHD centers on mucosal barrier repair, promotion of intestinal epithelial regeneration, and reduction of bacterial translocation driving inflammation.

8. Sourcing and Quality Verification

Apraglutide is not available as a registered pharmaceutical product in any jurisdiction as of the monograph revision date. The compound is available as a research-grade synthetic peptide from multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Probecchem Biochemicals, GlpBio, BocSci, and others) under CAS number 1295353-98-8, typically supplied as the trifluoroacetate (TFA) salt or the free base [29]. Supply is in milligram quantities as a lyophilized powder; pricing is in the range typical of custom synthetic peptides (substantially higher per milligram than small-molecule compounds, reflecting the cost of solid-phase peptide synthesis and HPLC purification).

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

- Analytical reversed-phase HPLC area-percent purity (ideally greater than 95 percent)
- Mass spectrometry confirmation of molecular weight (3,765.20 +/- 1.0 for the free base [M+H]⁺)
- Amino acid analysis confirming the presence of glycine at position 2, nor-leucine at position 10, D-phenylalanine at position 11, and leucine at position 16
- Peptide content determination by nitrogen analysis or quantitative amino acid analysis
- Endotoxin testing (Limulus amebocyte lysate or recombinant factor C assay) for any material intended for in vivo preclinical studies
- Counterion identification (TFA versus acetate) for formulation compatibility

Third-party analytical confirmation is appropriate for any investigation where dose-response precision is important. The research-grade apraglutide market is smaller than that of established peptides and the number of independent suppliers is limited; investigators should exercise due diligence on vendor certificates of analysis.

9. Reconstitution and Handling

Apraglutide as a lyophilized research-grade peptide should be reconstituted in sterile water for injection, phosphate-buffered saline (pH 7.4), or other physiological buffer appropriate for the intended application. For in vitro cell-based assays, reconstitution in dimethyl sulfoxide (DMSO) at concentrated stock (for example, 1 to 10 mM) followed by dilution into assay buffer is acceptable; the final DMSO concentration in the assay should not exceed 0.1 percent to avoid vehicle effects on cell viability and receptor pharmacology.

For subcutaneous administration in preclinical animal studies, reconstitution in sterile saline or phosphate-buffered saline at the target concentration (typically 0.1 to 1 mg/mL) is standard. The clinical formulation under development by Ironwood Pharmaceuticals is a solution for subcutaneous injection in prefilled devices, with specific excipient and buffer composition not publicly disclosed.

Storage of the lyophilized powder should be at minus 20 degrees Celsius or below, protected from moisture. Reconstituted solutions should be stored at 2 to 8 degrees Celsius and used within 7 to 14 days for research applications, or within 24 hours if reconstituted in non-bacteriostatic sterile water. Aliquoting of reconstituted stock into single-use volumes is recommended to avoid repeated freeze-thaw cycles, which can reduce peptide potency through aggregation and adsorption to container surfaces. Peptide solutions should be stored in low-binding polypropylene tubes or siliconized glass to minimize adsorptive losses.

The C-terminal amide of apraglutide confers somewhat greater chemical stability relative to C-terminal free acid peptides under physiological pH conditions. The norleucine substitution at position 10 (replacing methionine) eliminates oxidative degradation sensitivity, further improving stability of stock solutions and formulations.

10. Stack Interactions and Combinations

Apraglutide is a peptide that is degraded by general proteolysis and is not metabolized by cytochrome P450 enzymes. Accordingly, the classical cytochrome P450-mediated drug-drug interactions that dominate the interaction profile of small-molecule drugs are not expected. The principal interaction considerations are pharmacological rather than pharmacokinetic.

Parenteral nutrition and fluid management: In SBS-IF patients, apraglutide therapy improves intestinal absorption and may reduce parenteral support requirements. Clinical management protocols should include regular reassessment of parenteral support volume, composition, and frequency during apraglutide treatment to avoid fluid overload or electrolyte imbalance as absorptive capacity improves [5, 8].

Oral medications: Improved intestinal absorption during apraglutide therapy may increase the bioavailability of concurrently administered oral medications. Drugs with narrow therapeutic indices (warfarin, digoxin, phenytoin, theophylline, cyclosporine, tacrolimus) should be monitored during initiation and dose titration of apraglutide therapy, with dose adjustments guided by therapeutic drug monitoring [14, 30].

Other GLP-2 receptor agonists: Concurrent administration of apraglutide with teduglutide or glepaglutide is pharmacologically redundant and has not been studied. The combination would be expected to produce additive intestinotrophic effects but is not recommended in the absence of safety data.

GLP-1 receptor agonists: GLP-1 agonists (semaglutide, liraglutide, tirzepatide) are not contraindicated with apraglutide. However, the GLP-1 and GLP-2 receptor systems have opposing effects on gastric emptying and intestinal motility (GLP-1 slows gastric emptying; GLP-2 effects on motility are complex and context-dependent). The combination has not been formally studied in clinical trials. The SBS-IF patient population is unlikely to be co-prescribed GLP-1 agonists for metabolic indications.

Immunosuppressants in GvHD: In the STARGAZE trial, apraglutide was administered in combination with ruxolitinib (a JAK1/JAK2 inhibitor) and best available therapy without evidence of pharmacokinetic interaction or unexpected adverse events [10]. The combination was well tolerated, supporting the feasibility of concurrent use with immunosuppressive regimens in the GI aGVHD setting.

DPP-IV inhibitors: DPP-IV inhibitors (sitagliptin, vildagliptin, saxagliptin) would theoretically prolong the half-life of native GLP-2 but are not expected to substantially affect apraglutide pharmacokinetics, as apraglutide is already resistant to DPP-IV through the Gly2 substitution [1, 13].

11. Adverse Events and Safety Signal

11.1 Common adverse events

The adverse-event profile of apraglutide across the clinical development program has been consistent with the pharmacological mechanism of GLP-2 receptor agonism and the intestinotrophic effects on the gastrointestinal tract. In the Phase 1/2 open-label metabolic balance trial (n = 8), the most frequent treatment-related adverse events were [8]:

- Decreased gastrointestinal stoma output (75 percent)
- Stoma complications (75 percent)
- Nausea (62.5 percent)
- Flatulence (50 percent)
- Polyuria (37.5 percent)
- Abdominal pain (37.5 percent)

In the Phase 2 randomized crossover trial (n = 8), treatment-related adverse events included polyuria, decreased stoma output, stoma complications, decreased thirst, and edema, all mild to moderate in severity [11].

In the pivotal Phase 3 STARS trial (n = 163 dosed), the overall incidence of adverse events was similar between the apraglutide and placebo arms. The most commonly reported adverse events across both arms included nasopharyngitis, vomiting, diarrhea, and injection site reactions. Gastrointestinal tolerability adverse events were of low incidence and similar between treatment groups [5, 6]. The discontinuation rate due to adverse events was low: 3.6 percent in the apraglutide arm versus 1.9 percent in the placebo arm.

11.2 Adverse events of special interest

Injection site reactions: Injection site reactions were identified as areas of special interest in the safety monitoring program. The incidence was low and reactions were generally mild (erythema, pruritus, pain at the injection site) [5, 6].

Fluid and electrolyte shifts: Improved intestinal fluid absorption may produce polyuria, decreased stoma output, and changes in fluid balance that require adjustment of parenteral support. These are pharmacological effects rather than toxicities and are managed through clinical protocol-guided parenteral support reduction [8, 11].

Gastrointestinal events: Nausea, flatulence, abdominal pain, and stoma complications are consistent with the class effect of GLP-2R agonists and with changes in intestinal morphology and absorptive function. These events were predominantly mild to moderate and did not lead to treatment discontinuation in most patients [8, 11].

11.3 Serious adverse events

In the Phase 1/2 metabolic balance trial, one serious adverse event (abdominal pain requiring hospitalization) was reported; it resolved with dose reduction and rechallenge [8]. All 8 patients completed the trial. In the STARS trial, serious adverse events were reported at similar rates in the apraglutide and placebo arms, with no pattern suggestive of a drug-specific serious toxicity signal [5, 6].

11.4 Immunogenicity

Anti-apraglutide antibodies were detected in a small number of patients across the clinical program. In the Phase 1/2 metabolic balance trial, one of 8 patients developed low-titer anti-apraglutide antibodies with no relationship to adverse outcomes [8]. In the Phase 2 randomized trial, three of 8 patients developed antibodies, also without clinical consequences [11]. Immunogenicity monitoring has been included in the Phase 3 program; the incidence of treatment-emergent anti-drug antibodies and their clinical significance have not been fully reported for the STARS trial.

11.5 Long-term safety considerations

GLP-2 is a growth factor for the intestinal epithelium, and theoretical concerns exist regarding the potential for GLP-2R agonists to promote intestinal neoplasia with long-term use. This class effect concern has been characterized in the teduglutide clinical program and prescribing label, which includes recommendations for colonoscopic surveillance at baseline and at regular intervals during treatment.

Apraglutide would be expected to carry similar long-term surveillance recommendations if approved. No signals of intestinal neoplasia have been reported in the apraglutide clinical program to date, though the duration of follow-up is limited.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five GLP-2 receptor agonist candidates against apraglutide, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal GLP-2R ligands with substantive clinical or preclinical pharmacology programs in intestinal failure or related indications.

12.1 Teduglutide (Gattex/Revestive)

Mechanism: GLP-2 receptor agonist. [Gly2]hGLP-2(1-33), a single amino acid substitution (Gly2 for Ala2) conferring DPP-IV resistance. The minimal modification of the native sequence preserves full receptor activity [13, 14].

Development trajectory: Developed by NPS Pharmaceuticals and subsequently acquired by Takeda (through Shire). Approved by the FDA in December 2012 (Gattex) and by the EMA in August 2012 (Revestive) for the treatment of adults with SBS who are dependent on parenteral support. Extended approval to pediatric patients (1 year and older) in 2019 [14, 30].

Novelty: Low. Teduglutide is the first-generation GLP-2 analog with a single conservative amino acid substitution. The mechanism and compound class are well established.

Effect size: The STEPS and STEPS-2 pivotal trials demonstrated significant reductions in parenteral support volume. In the STEPS trial, 63 percent of teduglutide-treated patients achieved a 20 percent or greater reduction in parenteral support volume at 24 weeks versus 30 percent for placebo ($P = 0.002$). Enteral autonomy rates with long-term teduglutide treatment have been reported at approximately 5 to 10 percent in open-label extensions [14, 30].

Promising potential: Moderate. Teduglutide is the approved standard of care for SBS-IF and generates significant annual revenue. However, the requirement for daily subcutaneous injection is a substantial patient burden, and the next-genera-

tion analogs (apraglutide, glepaglutide) with less frequent dosing represent potential improvements [14].

Side-effect profile: Common adverse events include abdominal pain, nausea, catheter-related complications, intestinal obstruction, and injection site reactions. The prescribing label includes warnings for intestinal neoplasia risk (requiring colonoscopic surveillance), biliary and pancreatic disease, and fluid overload. The daily injection burden contributes to patient non-adherence [14, 30].

Overall validation: High. The compound is FDA- and EMA-approved with a mature clinical evidence base and extensive post-marketing experience. It is the benchmark against which all subsequent GLP-2 analogs are compared.

Comparison to apraglutide: Apraglutide offers a substantially longer half-life (72 hours versus 1.3 to 2 hours), enabling once-weekly versus daily dosing. In preclinical head-to-head comparisons, apraglutide demonstrated 37-fold lower clearance and approximately two-fold greater receptor potency [1]. The STARS trial effect size (25.5 percent PS volume reduction versus 12.5 percent placebo) is broadly comparable in magnitude to the STEPS trial results. The once-weekly dosing convenience and elimination of daily reconstitution steps represent a meaningful patient experience advantage.

12.2 Glepaglutide (Zealand Pharma)

Mechanism: GLP-2 receptor agonist. A GLP-2 analog with multiple amino acid modifications designed for twice-weekly subcutaneous dosing [19].

Development trajectory: Developed by Zealand Pharma. The Phase 3 EASE SBS-1 and EASE SBS-2 trials evaluated glepaglutide for SBS-IF with twice-weekly dosing. The EASE SBS-2 trial demonstrated significant reductions in parenteral support [19, 31].

Novelty: Low to moderate. The compound extends the GLP-2 analog class with a pharmacokinetic profile intermediate between teduglutide (daily) and apraglutide (weekly).

Effect size: The Phase 3 EASE SBS-2 trial with twice-weekly dosing demonstrated parenteral support volume reductions comparable to teduglutide and broadly similar to apraglutide. Enteral autonomy was achieved in 14 percent of glepaglutide-treated patients versus 0 percent on placebo [31].

Promising potential: Moderate. The compound has completed Phase 3 development and is under regulatory review. The twice-weekly dosing is an improvement over teduglutide but less convenient than once-weekly apraglutide.

Side-effect profile: Common adverse events include injection site reactions, nausea, abdominal distension, and vomiting. In preclinical characterization, glepaglutide was reported to have lower selectivity for GLP-2R versus the related GLP-1 receptor compared to apraglutide and teduglutide, which could theoretically contribute to off-target effects [1].

Overall validation: Moderate to high. Phase 3 data support efficacy. Regulatory review is pending.

Comparison to apraglutide: Apraglutide has a longer half-life, lower clearance, greater receptor selectivity, and less frequent dosing (once-weekly versus twice-weekly). The head-to-head preclinical PK comparison showed apraglutide with approximately 10-fold lower clearance and 10-fold longer half-life than glepaglutide [1]. Both compounds represent improvements over teduglutide; apraglutide offers the greatest dosing convenience.

12.3 Native GLP-2 (human, recombinant)

Mechanism: The endogenous ligand for the GLP-2 receptor. Produced by post-translational processing of proglucagon in enteroendocrine L-cells of the distal ileum and colon [13, 15].

Development trajectory: Native GLP-2 was characterized by Daniel Drucker and colleagues at the University of Toronto in the mid-1990s as an intestinotrophic factor. Exogenous subcutaneous native GLP-2 was studied in SBS patients and demonstrated proof of concept for GLP-2R agonism in improving intestinal absorption [13, 32].

Novelty: High (historically). Native GLP-2 established the entire field of GLP-2 receptor pharmacology and intestinotrophic therapy.

Effect size: Modest improvements in intestinal absorption in early clinical studies with multiple daily subcutaneous injections, limited by the extremely short plasma half-life of approximately 7 minutes due to DPP-IV cleavage [13, 32].

Promising potential: None as a therapeutic candidate. The rapid degradation makes native GLP-2 impractical for clinical use. Its role is as the reference compound for the analog class.

Side-effect profile: Mild gastrointestinal effects consistent with the class.

Overall validation: High as a research tool and proof-of-concept compound. Not viable as a therapeutic.

Comparison to apraglutide: Apraglutide was rationally designed to overcome the pharmacokinetic limitations of native GLP-2 while retaining or exceeding its receptor potency and selectivity. The 93-fold reduction in clearance and the practical shift from multiple daily injections to once-weekly dosing represent the full realization of the GLP-2 analog medicinal chemistry program [1].

12.4 Dapiglutide

Mechanism: Dual GLP-1 and GLP-2 receptor agonist. A hybrid peptide designed to simultaneously activate both GLP-1R and GLP-2R, combining the metabolic effects of GLP-1 agonism (glucose regulation, appetite suppression) with the intestinotrophic effects of GLP-2 agonism [33].

Development trajectory: Preclinical development. Reiner et al. (2022) demonstrated that dapiglutide attenuated intestinal insufficiency in a murine model of short bowel following massive small bowel resection [33]. The compound is in early-stage development without published clinical trial data.

Novelty: High. The dual GLP-1/GLP-2 agonist mechanism is a novel approach that addresses both the intestinal and metabolic consequences of SBS.

Effect size: Preclinical only. Mouse model data demonstrated improvements in intestinal adaptation following resection. Effect sizes in animal models do not translate predictively to human clinical effect.

Promising potential: Low to moderate as a near-term therapeutic; high as a research concept. The dual-agonist approach may prove clinically important but has not advanced to human studies.

Side-effect profile: Preclinical only. No human safety data. The GLP-1 agonist component would be expected to produce nausea, vomiting, and appetite suppression that could be counterproductive in SBS patients who need to maximize oral

intake.

Overall validation: Low. Preclinical only.

Comparison to apraglutide: Dapiglutide represents a conceptually distinct approach (dual agonism versus selective GLP-2R agonism). Apraglutide has the advantages of advanced clinical development, established safety data, and a mechanism specifically tailored to the intestinotrophic endpoint without the potentially counterproductive GLP-1R-mediated appetite suppression and delayed gastric emptying.

12.5 Elsiglutide

Mechanism: GLP-2 receptor agonist. A GLP-2 analog studied for the prevention of chemotherapy-induced diarrhea rather than for SBS-IF [34].

Development trajectory: Developed by Helsinn. Elsiglutide was evaluated in Phase 2 and Phase 3 clinical trials for the prevention of chemotherapy-induced diarrhea in cancer patients. The compound exploits the GLP-2R agonist mechanism to promote intestinal mucosal integrity and reduce the diarrheal toxicity of cytotoxic chemotherapy, a different clinical context from the SBS-IF focus of apraglutide and teduglutide.

Novelty: Moderate. The application of GLP-2R agonism to chemotherapy-induced diarrhea represents a novel indication rather than a novel mechanism.

Effect size: Phase 3 data have been mixed, with the compound not consistently demonstrating clinically meaningful reductions in severe diarrhea across tumor types and chemotherapy regimens [34].

Promising potential: Low. Clinical development has not produced registration-quality efficacy data for the chemotherapy-induced diarrhea indication.

Side-effect profile: The compound was generally well tolerated in clinical trials, with adverse events consistent with the GLP-2R agonist class.

Overall validation: Low to moderate. The compound has produced clinical data but not a positive Phase 3 outcome.

Comparison to apraglutide: Elsiglutide targets a different clinical indication (chemotherapy-induced diarrhea versus SBS-IF). The two compounds are not direct competitors but illustrate the breadth of the GLP-2R agonist therapeutic landscape.

Apraglutide has a substantially more mature clinical development program and a stronger efficacy evidence base in its target indication.

12.6 Comparator summary

The five compounds span the GLP-2 receptor agonist landscape from the endogenous ligand through first- and next-generation therapeutic analogs to novel dual-agonist and alternative-indication approaches. **Teduglutide** is the approved standard of care with mature validation but limited by daily dosing. **Glepaglutide** extends the class to twice-weekly dosing with Phase 3 data. **Native GLP-2** is the historical reference compound that established the field. **Dapiglutide** represents a novel dual-agonist concept in early preclinical development. **Elsiglutide** demonstrates the breadth of GLP-2R agonist applications but has not achieved registration for its target indication.

Apraglutide occupies a leading position in this comparator landscape through the combination of: the longest half-life and lowest clearance in the class (enabling once-weekly dosing, the least frequent administration among all GLP-2 analogs in or near clinical use); retained or superior receptor potency and selectivity; positive Phase 3 data in the largest SBS-IF trial conducted to date; the unique preclinical demonstration of intestinal lengthening in addition to mucosal surface area increase; and the first demonstration of significant energy absorption improvement across the full SBS patient spectrum by bomb calorimetry. The principal limitation is the current regulatory status: the FDA requirement for a confirmatory Phase 3 trial (STARS-2) extends the timeline to potential approval to approximately 2029, while teduglutide is already approved and glepaglutide may achieve regulatory clearance sooner.

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