

RESEARCH MONOGRAPH . COMPOUND PROFILE

Relamorelin

A synthetic pentapeptide ghrelin analog developed as a selective growth hormone secretagogue receptor agonist with approximately sixfold greater potency than native ghrelin, advanced through Phase 2 and Phase 3 clinical trials for diabetic gastroparesis, chronic idiopathic constipation, and anorexia nervosa.

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ABSTRACT

Relamorelin (RM-131, BIM-28131) is a synthetic pentapeptide analog of ghrelin that activates the growth hormone secretagogue receptor type 1a (GHSR-1a) with approximately three- to sixfold greater binding affinity and functional potency than native human ghrelin, and with substantially enhanced plasma stability and a terminal elimination half-life of approximately 4.5 to 19.4 hours depending on dose and measurement interval. The compound was originally synthesized by Ipsen as BIM-28131 and subsequently developed by Rhythm Pharmaceuticals (as RM-131), Motus Therapeutics, Allergan, and AbbVie for gastrointestinal motility disorders, principally diabetic gastroparesis, chronic idiopathic constipation, and anorexia nervosa. Relamorelin accelerates gastric emptying through activation of ghrelin receptors expressed on enteric neurons, interstitial cells of Cajal, and gastric smooth muscle, producing dose-dependent increases in antral contractile frequency and propagated colonic contractions without inhibition of gastric accommodation or induction of early satiation. In nonclinical studies, the compound reversed morphine-induced gastroparesis in Sprague-Dawley rats at potencies approximately 100-fold greater than native ghrelin and stimulated gastrointestinal transit throughout the small and large intestine. In clinical trials, relamorelin administered subcutaneously at 10 to 100 micrograms once or twice daily significantly accelerated gastric emptying half-time (mean difference of approximately 8 to 11 minutes versus placebo), reduced vomiting frequency by approximately 60 to 75 percent in diabetic gastroparesis populations with documented delayed gastric emptying, and improved composite symptom scores for

nausea, bloating, abdominal pain, and early satiety. A Phase 2 trial in chronic idiopathic constipation demonstrated significant acceleration of colonic transit at 32 and 48 hours and increased spontaneous bowel movement frequency over 14 days of treatment. A proof-of-concept randomized trial in outpatient women with anorexia nervosa demonstrated significant reduction in gastric emptying time (median 58 versus 85 minutes) and a trend toward weight gain after four weeks of treatment. The principal adverse events observed across clinical programs were hyperglycemia (reflecting accelerated nutrient delivery to the small intestine in diabetic populations), diarrhea, headache, and dizziness, with no clinically significant injection site reactions. Growth hormone, prolactin, and cortisol elevations were observed as expected pharmacodynamic consequences of GHSR-1a activation. Allergan initiated a Phase 3 program (PLEDGE) comprising two pivotal 12-week randomized controlled trials in diabetic gastroparesis beginning in 2018; however, in September 2020, the program was terminated following the AbbVie acquisition of Allergan, and the compound is not currently in active clinical development. Relamorelin is not approved by any regulatory authority. It remains available as a research-grade compound from multiple chemical suppliers and is the subject of ongoing academic interest as both a pharmacological tool for ghrelin receptor biology and a potential therapeutic candidate for gastrointestinal dysmotility syndromes. This monograph reviews the chemistry, structure, and synthesis of relamorelin; the molecular pharmacology at the GHSR-1a receptor; comprehensive pharmacokinetics; preclinical gastrointestinal pharmacology; the clinical evidence base across diabetic gastroparesis, chronic constipation, and anorexia nervosa indications; sourcing and quality verification; reconstitution and handling; stack

interactions; adverse events and safety signals; and a comparative assessment of five gastroparesis therapeutic candidates against relamorelin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Relamorelin (proposed; not yet assigned by WHO INN).

Development codes: RM-131 (Rhythm Pharmaceuticals), BIM-28131 (Ipsen), BIM-28163 (Ipsen salt form).

Chemical Abstracts Service registry number: 661472-41-9 (free base). The acetate salt (CAS 1809080-14-5) and trifluoroacetate salt are also commercially available from research suppliers.

DrugBank identifier: DB12678.

Structural class: Relamorelin is classified as a synthetic hybrid pentapeptide containing modified amino acid residues that confer resistance to enzymatic degradation while preserving high-affinity binding to the growth hormone secretagogue receptor type 1a (GHSR-1a). The compound is a ghrelin mimetic; it reproduces the receptor-activating pharmacophore of the N-terminal active fragment of ghrelin (residues 1 through 5) with non-natural amino acid substitutions that enhance metabolic stability and receptor potency [1, 2].

1.2 Structural class and chemistry

Relamorelin is a pentapeptide synthetic ghrelin analog. The precise amino acid sequence incorporates non-natural residues including D-amino acids and cyclic constraints that differentiate it from the natural octanoylated 28-amino-acid ghrelin peptide. The molecular structure has been partially disclosed in patent literature but is not fully in the public domain; the rights holder (originally Ipsen, subsequently Rhythm Pharmaceuticals, Motus Therapeutics, and Allergan/AbbVie) has maintained proprietary protection over the complete stereochemical and sequential description [2, 3].

Molecular formula: C₄₃H₅₀N₈O₅S (free base).

Molecular weight: 790.98 g/mol (free base).

Physical properties: White to off-white lyophilized powder. Soluble in water and in dimethyl sulfoxide. The compound is supplied as the free base, the acetate salt, or the trifluoroacetate salt depending on supplier formulation. Stability is maintained under refrigerated conditions (2 to 8 degrees Celsius) in solid form and in aqueous solution for at least 14 days.

Key structural features: The pentapeptide contains a benzo[b]thiophene moiety, an indole ring system (tryptophan-derived), a phenyl group (phenylalanine-derived), and a 4-carbamoylpiperidine terminus. These structural elements contribute to the enhanced lipophilicity, receptor binding affinity, and resistance to peptidase degradation relative to native ghrelin [1, 3].

1.3 Synthesis

The synthesis of relamorelin proceeds by solid-phase or solution-phase peptide coupling methodologies employing standard Fmoc (9-fluorenylmethyloxycarbonyl) or Boc (tert-butyloxycarbonyl) protection strategies for the non-natural amino acid building blocks. The key synthetic challenges are the incorporation of the benzo[b]thiophene-containing residue with correct stereochemistry, the formation of the piperidine-3-carboxamide N-terminal cap, and the 4-carbamoylpiperidine C-terminal amide. Purification is accomplished by preparative reversed-phase high-performance liquid chromatography, with identity confirmation by mass spectrometry and purity assessment by analytical HPLC. The compound is manufactured at research scale (milligram to gram quantities) by multiple peptide synthesis contract organizations and is available from commercial research suppliers at greater than 95 percent purity by HPLC [3, 4].

2. Abstract

Relamorelin (RM-131, BIM-28131) is a synthetic pentapeptide ghrelin receptor agonist that binds and activates the growth hormone secretagogue receptor type 1a (GHSR-1a) with approximately three- to sixfold greater potency than native human ghrelin in functional cellular assays measuring intracellular calcium mobilization [1, 2]. The compound was developed as a gastrocolokinetic agent, a term introduced to describe its capacity to accelerate motility throughout the gastrointestinal tract from the gastric antrum through the colon, distinguishing it from pure gastroprokinetics that act predominantly on gastric emptying [5].

The principal therapeutic indication studied in clinical trials is diabetic gastroparesis, a condition affecting approximately 20 to 40 percent of patients with long-standing type 1 or type 2 diabetes mellitus and characterized by delayed gastric emptying in the absence of mechanical obstruction, with symptoms including nausea, vomiting, abdominal pain, bloating, and early satiety. Current pharmacotherapy for gastroparesis is limited to metoclopramide (the only FDA-approved agent, with a black-box warning for tardive dyskinesia), domperidone (available outside the United States), and erythromycin (motilin receptor agonist with tachyphylaxis). Relamorelin represented a mechanistically novel approach through direct activation of ghrelin receptors on the enteric nervous system and interstitial cells of Cajal [6, 7].

In Phase 2a and 2b clinical trials enrolling a combined total of approximately 600 patients with diabetic gastroparesis, subcutaneous relamorelin at doses of 10 to 100 micrograms once or twice daily produced statistically significant acceleration of gastric emptying, reduction in vomiting frequency and severity, and improvement in composite gastroparesis symptom scores compared to placebo over treatment periods of 4 to 12 weeks [8, 9, 10]. A Phase 2 trial in 48 women with chronic idiopathic constipation demonstrated significant acceleration of colonic transit and increased spontaneous bowel movement frequency over 14 days [11]. A proof-of-concept trial in 22 outpatient women with anorexia nervosa demonstrated significant acceleration of gastric emptying and a trend toward weight gain at 4 weeks [12].

The PLEDGE Phase 3 program, comprising two identical pivotal 12-week randomized controlled trials (RLM-MD-01 and RLM-MD-02) and supporting long-term safety and extension studies, was initiated by Allergan in 2018 and expanded in May 2019 [13]. Following the acquisition of Allergan by AbbVie in May 2020, the Phase 3 program was terminated in September 2020. Relamorelin is not approved by any regulatory authority and is not in active commercial development as of the most recent monograph revision.

The compound remains of substantial scientific interest as a pharmacological tool for investigating ghrelin receptor biology in the gastrointestinal tract, as a reference agonist for GHSR-1a structure-activity relationship studies, and as a potential therapeutic candidate should the gastroparesis clinical development pathway be resumed. This monograph provides a comprehensive review of the chemistry, pharmacology, pharmacokinetics, preclinical and clinical evidence, handling considerations, and comparative assessment of relamorelin in the context of the gastrointestinal motility therapeutic landscape.

3. Discovery and Development History

3.1 Origin

Relamorelin was originally synthesized at Ipsen (formerly Beaufour-Ipsen) as part of a medicinal chemistry program to develop potent, metabolically stable analogs of the natural hormone ghrelin for potential therapeutic applications in growth hormone deficiency, cachexia, and gastrointestinal motility disorders. The compound was designated BIM-28131 in the Ipsen internal numbering system. The design strategy involved systematic replacement of the natural amino acid residues in the ghrelin N-terminal pharmacophore with non-natural analogs conferring resistance to dipeptidyl peptidase IV (DPP-IV) and other serine proteases responsible for rapid ghrelin inactivation in plasma [1, 2].

The key advance was the identification of a pentapeptide scaffold that retained full agonist activity at GHSR-1a while eliminating the octanoyl (C8 fatty acid) modification on serine-3 that is required for activity of native ghrelin but that also drives the short plasma half-life and poor bioavailability of the natural hormone. Relamorelin achieves receptor activation through direct hydrophobic contacts between the benzo[b]thiophene and indole ring systems and the transmembrane binding pocket of the receptor, bypassing the requirement for the acyl chain [1, 3].

3.2 Transfer to Rhythm Pharmaceuticals

Ipsen licensed or transferred the relamorelin program to Rhythm Pharmaceuticals (later Rhythm Health), a venture-backed biotechnology company formed in 2013 with the specific purpose of developing ghrelin-based therapeutics for gastrointestinal and metabolic disorders. Rhythm designated the compound RM-131 and advanced it through Phase 1 healthy volunteer studies and Phase 2 clinical trials in diabetic gastroparesis, chronic constipation, and anorexia nervosa. Rhythm investors included MPM Capital, New Enterprise Associates, Third Rock Ventures, Ipsen, and Pfizer Ventures [14].

3.3 Acquisition by Allergan

In 2016, Allergan (then an independent specialty pharmaceutical company) acquired Motus Therapeutics, the entity that held the relamorelin clinical development program, for an upfront payment of approximately 200 million United States dollars plus milestone payments. The acquisition was driven by positive Phase 2a and Phase 2b results demonstrating gastric emptying acceleration and symptom improvement in diabetic gastroparesis. Allergan designated relamorelin as the lead asset in its gastrointestinal pipeline and initiated the PLEDGE Phase 3 program in 2018 [13, 15].

3.4 Phase 3 program and termination

The PLEDGE program ultimately comprised five studies: two identical pivotal 12-week efficacy trials (RLM-MD-01 and RLM-MD-02), a long-term open-label safety extension (following participants for up to 5 years), and supporting pharmacokinetic and special-population studies. In May 2019, Allergan reported that recruitment was ongoing for the pivotal trials. In January 2020, AbbVie completed its acquisition of Allergan for approximately 63 billion United States dollars. In September and October 2020, the Phase 3 and Phase 3b relamorelin trials were terminated across multiple countries; the European Medicines Agency recorded discontinuation of the pediatric investigation plan in September 2020. No Phase 3 efficacy data have been published. The reasons for termination have not been publicly disclosed in detail but are understood to reflect portfolio prioritization decisions by AbbVie rather than safety signals or definitive efficacy failure [13, 16].

3.5 Current status

As of the most recent monograph revision, relamorelin is not in active commercial clinical development. The compound is not approved by any regulatory authority for any indication. Research-grade material remains available from multiple suppliers, and academic publications continue to reference the compound in reviews of gastroparesis therapeutics, ghrelin receptor biology, and gastrointestinal prokinetic pharmacology.

4. Mechanism of Action

4.1 Ghrelin and the growth hormone secretagogue receptor

Ghrelin is a 28-amino-acid peptide hormone produced predominantly by X/A-like enteroendocrine cells of the gastric fundus. It is the endogenous ligand for the growth hormone secretagogue receptor type 1a (GHSR-1a), a seven-transmembrane G protein-coupled receptor expressed in the hypothalamus (arcuate nucleus, ventromedial hypothalamus), pituitary somatotrophs, vagal afferent neurons, enteric neurons of the myenteric and submucosal plexuses, interstitial cells of Cajal throughout the gastrointestinal tract, and at lower density in cardiac tissue and immune cells [6, 17].

Native ghrelin requires post-translational octanoylation (addition of an 8-carbon fatty acid chain) on serine residue 3 for receptor binding and activation. This modification is catalyzed by ghrelin O-acyltransferase (GOAT) and is the basis for ghrelin's short plasma half-life (approximately 10 to 30 minutes) as circulating esterases rapidly cleave the acyl chain to produce inactive des-acyl ghrelin [17].

4.2 Relamorelin receptor pharmacology

Relamorelin binds GHSR-1a with approximately threefold greater affinity than native acylated ghrelin in radioligand displacement assays and activates the receptor with approximately sixfold greater potency in functional calcium mobilization assays [1, 2]. The compound acts as a full agonist, producing maximal receptor activation comparable to saturating concentrations of native ghrelin. Selectivity for GHSR-1a over related G protein-coupled receptors (including the unliganded constitutively active GHSR-1b splice variant, motilin receptor, neurotensin receptors, and other peptide GPCRs) has been characterized in the patent literature and is reported as high, though comprehensive published selectivity data across a broad receptor panel are limited [1, 3].

Receptor activation by relamorelin initiates the canonical GHSR-1a signaling cascade: coupling to Gq/11 proteins, activation of phospholipase C-beta, generation of inositol 1,4,5-trisphosphate and diacylglycerol, mobilization of intracellular cal-

cium from endoplasmic reticulum stores, and activation of protein kinase C. In enteric neurons and interstitial cells of Cajal, this calcium mobilization drives increased contractile activity and pacemaker depolarization frequency [6, 18].

4.3 Gastrointestinal motility mechanism

The gastrocolokinetic effect of relamorelin is mediated through multiple anatomical targets. In the gastric antrum, GHSR-1a activation on excitatory motor neurons of the myenteric plexus increases acetylcholine release onto circular smooth muscle, increasing antral contraction frequency without significant effects on contraction amplitude [19]. In the gastric corpus, the compound does not inhibit gastric accommodation (the reflex relaxation of the proximal stomach that prevents intragastric pressure elevation during meal ingestion), a finding that differentiates relamorelin from agents like erythromycin that can impair accommodation and induce early satiation [19].

In the small intestine, relamorelin accelerates transit through activation of GHSR-1a on myenteric neurons and possibly on interstitial cells of Cajal of the small bowel. In the colon, the compound stimulates propagated (high-amplitude) contractions without alteration of background irregular contractile activity, a pharmacological profile consistent with enhanced propulsive motility rather than generalized spasm [11, 20].

4.4 Growth hormone secretagogue activity

As a GHSR-1a agonist, relamorelin stimulates growth hormone release from anterior pituitary somatotrophs through the hypothalamic-pituitary growth hormone axis. Subcutaneous administration in humans produces dose-dependent elevations in plasma growth hormone, prolactin, and cortisol concentrations [2, 5]. The growth hormone release is an expected on-target pharmacodynamic effect rather than a therapeutic goal in the gastroparesis indication, and represents both a biomarker of receptor engagement and a consideration for long-term safety monitoring. The magnitude of growth hormone elevation at therapeutic doses for gastroparesis (10 to 100 micrograms subcutaneously) is modest and does not approach the supraphysiological levels associated with exogenous growth hormone administration.

4.5 Appetite and metabolic effects

Ghrelin is the principal circulating orexigenic hormone, and GHSR-1a activation in the arcuate nucleus stimulates appetite through activation of neuropeptide Y/agouti-related peptide neurons. Relamorelin administration in preclinical studies increased food intake and induced weight gain in normal mice and rats in a dose-dependent manner, with balanced increases in both fat and lean mass [2, 21]. In clinical studies, the appetite-stimulating effect was observed in the anorexia nervosa trial, where three participants discontinued due to increased hunger, and may contribute to the weight gain trend observed in that population [12]. Central nervous system penetration of relamorelin in rats is low (brain availability approximately 0.015 percent of plasma at 5 mg/kg), suggesting that appetite effects in humans at therapeutic doses may be mediated predominantly through vagal afferent signaling rather than direct hypothalamic receptor activation [2].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Relamorelin is administered by subcutaneous injection. Following subcutaneous administration, the compound is rapidly absorbed with a median time to peak plasma concentration (T_{max}) of approximately 0.74 hours (range 0.27 to 1.02 hours) across all dose groups studied in single-ascending and multiple-ascending dose Phase 1 studies [2, 5]. The rapid absorption is consistent with the low molecular weight (791 Da) and moderate lipophilicity of the pentapeptide. Oral bioavailability has not been formally characterized in published studies but is expected to be low given the peptide nature of the compound, and all clinical development has used the subcutaneous route.

5.2 Distribution

Relamorelin exhibits two-compartment pharmacokinetics following subcutaneous administration, with rapid initial distribution followed by a slower elimination phase. Plasma protein binding in vitro is high, ranging from 83 to 96 percent with no substantial differences across rat, dog, and human sera [2, 5]. The volume of distribution has not been reported in published clinical pharmacokinetic analyses. Central nervous system penetration is low in preclinical rat studies (approximately 0.015 percent of administered dose), consistent with limited blood-brain barrier permeability of the peptide [2].

5.3 Metabolism and elimination

Relamorelin is metabolized by peptidases and proteases, though the enhanced stability conferred by the non-natural amino acid substitutions substantially prolongs the plasma half-life relative to native ghrelin. The terminal elimination half-life in humans is dose-dependent: at lower doses (10 to 30 micrograms), the measurable terminal half-life is approximately 4.5 hours; at higher doses (100 micrograms and above), where plasma concentrations remain above the lower limit of quantifica-

tion for longer periods, the terminal half-life measured over 72 hours is approximately 19.4 hours [2, 5]. This prolonged terminal phase supports once-daily or twice-daily dosing regimens.

The metabolic pathway has not been fully characterized in published literature. The compound does not undergo cytochrome P450-mediated metabolism to a significant extent (consistent with its peptide structure), and drug-drug interactions through CYP inhibition or induction are not anticipated. Renal elimination of intact peptide is expected to be minimal given the high protein binding and peptide nature of the compound.

5.4 Dose-response pharmacokinetics

In the Phase 1 single-ascending dose study, relamorelin pharmacokinetics were approximately dose-proportional across the 10 to 300 microgram dose range. Multiple-dose administration over 10 days did not produce clinically meaningful accumulation at the once-daily regimen, consistent with the shorter effective half-life (4.5 hours) dominating the steady-state pharmacokinetics at therapeutic doses [2, 5].

5.5 Routes of administration

All clinical development has employed subcutaneous injection, typically administered in the abdominal wall. The subcutaneous route provides rapid and reproducible absorption, avoids first-pass hepatic metabolism, and is consistent with the self-administration paradigm used for other peptide therapeutics (insulin, GLP-1 receptor agonists). No clinically significant injection site reactions have been reported across the Phase 1, 2a, and 2b clinical programs, suggesting good local tolerability of the formulation [10, 22].

5.6 Special populations

Specific pharmacokinetic studies in renal impairment, hepatic impairment, and pediatric populations have not been published. The PLEDGE Phase 3 program included plans for special-population pharmacokinetic characterization, but these studies were not completed prior to program termination.

6. Preclinical Pharmacology

6.1 In vitro receptor characterization

Relamorelin activates GHSR-1a in heterologous expression systems (HEK293 and CHO cells stably expressing human GHSR-1a) with an EC₅₀ for intracellular calcium mobilization approximately sixfold lower than native acylated ghrelin [1, 2]. The compound acts as a full agonist with intrinsic activity comparable to ghrelin at saturating concentrations. Binding affinity at the receptor (K_i) is approximately threefold greater than ghrelin in radioligand displacement assays using [125I]-ghrelin [1].

In human colon circular smooth muscle cells in vitro, relamorelin hyperpolarized the resting membrane potential, demonstrating direct functional effects on colonic smooth muscle that may contribute to the gastrocolokinetic profile independent of neural activation [20].

6.2 Gastric emptying in rodent models

In normal Sprague-Dawley rats, relamorelin dose-dependently accelerated gastric emptying of a semi-solid meal. In the morphine-induced gastroparesis model, relamorelin reversed the delayed gastric emptying with approximately 100-fold greater potency than native human ghrelin, establishing the compound as a substantially more potent prokinetic agent than the endogenous hormone [2, 5].

In nonclinical comparative pharmacology studies, the effects of relamorelin on gastric emptying were reported to be 15- to 130-fold more potent than natural ghrelin depending on the model system and endpoint measured [5].

6.3 Colonic transit

Ghrelin receptors are expressed throughout the gastrointestinal tract, with receptor density in the rodent intestine actually higher in the small and large intestine than in the stomach [20]. Relamorelin accelerated colonic transit in rodent models, con-

sistent with the gastrocolokinetic (rather than purely gastroprokinetic) profile that distinguishes the compound from motilin receptor agonists such as erythromycin [5, 11].

6.4 Food intake and body composition

Relamorelin increased food intake and induced weight gain in normal C57BL/6J mice and Sprague-Dawley rats in a dose-dependent manner. The weight gain reflected balanced increases in both fat mass and lean mass, consistent with the anabolic effects of growth hormone pathway activation combined with increased caloric intake [2, 21].

6.5 Growth hormone release

In preclinical models, relamorelin produced dose-dependent growth hormone release from the anterior pituitary, confirming on-target GHSR-1a activation. The growth hormone response was used as a pharmacodynamic biomarker in early clinical development to confirm receptor engagement at doses selected for gastrointestinal motility endpoints [2, 5].

7. Clinical Evidence Base

7.1 Phase 1 healthy volunteer studies

Phase 1 single-ascending and multiple-ascending dose studies in healthy volunteers established the safety, tolerability, pharmacokinetics, and pharmacodynamic profile of subcutaneous relamorelin at doses from 1 to 600 micrograms. The compound was well tolerated, produced dose-dependent growth hormone elevations confirming receptor engagement, and demonstrated no clinically significant adverse events or injection site reactions at doses up to 300 micrograms [2, 5].

Nelson et al. (2016) conducted a placebo-controlled, double-blind, randomized study in 16 healthy volunteers comparing 30 micrograms subcutaneous relamorelin to placebo. Relamorelin significantly increased the number of distal antral contractions during 0 to 60 minutes postmeal ($p = 0.022$), with effects most pronounced in the first two 15-minute periods ($p = 0.005$ and 0.015 for 0 to 15 and 16 to 30 minutes, respectively). The compound did not significantly alter fasting or postprandial gastric volumes, gastric accommodation, or satiation volumes and symptoms [19]. The preservation of gastric accommodation and absence of increased satiation supported advancement to the gastroparesis population, where inhibition of accommodation would be counterproductive.

7.2 Phase 2a diabetic gastroparesis (Shin et al. 2016)

The Phase 2a study was a double-blind, randomized, placebo-controlled trial of 204 patients with type 1 or type 2 diabetes mellitus and documented delayed gastric emptying (by scintigraphy or breath test) with moderate to severe gastroparesis symptoms, conducted at 27 clinical centers [8]. Patients were randomized 1:1:1 to subcutaneous placebo, relamorelin 10 micrograms once daily, or relamorelin 10 micrograms twice daily for 4 weeks.

Twice-daily relamorelin significantly accelerated gastric emptying ($p < 0.03$ versus placebo) and reduced vomiting frequency by approximately 60 percent and vomiting severity compared to placebo (p less than or equal to 0.033). In the subgroup of 119 patients (58.3 percent) with baseline vomiting, twice-daily relamorelin

significantly reduced gastric emptying half-time and vomiting, as well as nausea, abdominal pain, bloating, and early satiety compared to placebo (composite symptom score, $p = 0.043$) [8].

No overall safety concerns were identified. The most common treatment-emergent adverse events in relamorelin-treated patients were headache and worsening of pre-existing hyperglycemia.

7.3 Phase 2b diabetic gastroparesis (Camilleri et al. 2017)

The Phase 2b study was a 12-week randomized, double-blind, placebo-controlled trial of 393 patients with diabetes mellitus and moderate to severe gastroparesis symptoms, defined as recent vomiting and delayed gastric emptying (13C-spirulina gastric emptying breath test half-time of 79 minutes or greater) [9, 10]. Patients were randomized to subcutaneous placebo, relamorelin 10 micrograms, 30 micrograms, or 100 micrograms twice daily.

All four symptoms of diabetic gastroparesis (composite and individual symptom scores) were significantly reduced over the 12-week study period in all three relamorelin dose groups compared to placebo (all $p < 0.05$, based on longitudinal analysis). Relamorelin significantly accelerated gastric emptying from baseline compared to placebo (by 12 percent; $p < 0.05$ for the 10 and 30 microgram groups; $p = 0.051$ for the 100 microgram group) [9].

The prespecified primary endpoint of reduction in vomiting episodes per week did not achieve statistical significance owing to an unusually high placebo response rate (approximately 70 percent reduction in vomiting in the placebo group), although the relamorelin groups showed an average 75 percent reduction in vomiting [9].

Dose-related worsening of glycemic control was observed in 14.5 percent of relamorelin-treated patients, with hyperglycemia events distributed as 3 on placebo, 8 on 10 micrograms, 17 on 30 micrograms, and 17 on 100 micrograms. Some patients required insulin or other diabetes medication dose adjustments [9, 10].

7.4 Pooled safety analysis (Phase 2a and 2b)

A pooled safety analysis across Phase 2a and 2b trials in diabetic gastroparesis (published by Acosta et al. 2020) evaluated the overall safety of relamorelin in approximately 400 relamorelin-treated patients [22]. The analysis confirmed the favorable injection-site tolerability (no clinically important injection site reactions), identified hyperglycemia and diarrhea as the principal treatment-emergent adverse events, and reported no new safety signals relative to the individual trial reports. The hyperglycemia signal was attributed to accelerated gastric emptying delivering nutrients to the absorptive small intestine more rapidly, with consequent earlier and higher postprandial glucose excursions in patients whose antidiabetic regimens were optimized for their delayed baseline gastric emptying rate [22].

7.5 Chronic idiopathic constipation (Acosta et al. 2015)

A Phase 2 randomized, double-blind, placebo-controlled trial evaluated relamorelin 100 micrograms subcutaneously daily for 14 days in 48 female patients with chronic constipation meeting Rome III criteria, conducted at two Mayo Clinic sites [11]. Relamorelin significantly accelerated gastric emptying half-time, small-bowel transit time, and colonic transit at 32 and 48 hours compared to placebo. The compound increased the number of spontaneous bowel movements and accelerated the time to first bowel movement after the first dose compared to placebo, but did not affect stool form [11].

A companion mechanistic study demonstrated that relamorelin stimulates propagated colonic contractions without alteration of background irregular contractions, consistent with enhanced propulsive motility rather than generalized colonic stimulation [20].

7.6 Anorexia nervosa (Fazeli et al. 2018)

A proof-of-concept randomized, double-blind, placebo-controlled trial evaluated relamorelin 100 micrograms subcutaneously daily for 4 weeks in 22 outpatient women with anorexia nervosa, conducted at Massachusetts General Hospital Clinical Research Center between March 2013 and February 2015 [12]. Ten participants were randomized to relamorelin and 12 to placebo.

Gastric emptying time was significantly shorter in relamorelin-treated participants (median 58 minutes) compared to placebo (median 85 minutes; $p = 0.03$). There was a trend toward weight gain in the relamorelin group (0.86 plus or minus 0.4 kg) compared to placebo (0.04 plus or minus 0.28 kg; $p = 0.07$). Three participants randomized to relamorelin discontinued due to reported feelings of increased hunger [12]. The study supported further investigation of ghrelin agonism in anorexia nervosa but was insufficiently powered to demonstrate definitive weight gain.

7.7 PLEDGE Phase 3 program

The PLEDGE Phase 3 program comprised two identical, pivotal, 12-week, randomized, double-blind, placebo-controlled studies (RLM-MD-01, ClinicalTrials.gov NCT03426345; and RLM-MD-02, NCT03383146) evaluating relamorelin versus placebo in adults with diabetic gastroparesis [13]. Additional studies included a long-term open-label safety extension (52-week active treatment followed by up to 5-year follow-up) and supporting pharmacokinetic and special-population investigations.

Allergan reported active recruitment as of May 2019. Following the AbbVie acquisition of Allergan, both pivotal trials were terminated in September to October 2020. No Phase 3 efficacy or safety results have been reported publicly. The termination does not constitute a finding of inefficacy or safety concern; the compound had demonstrated consistent gastrointestinal motility effects and symptom improvement across the Phase 2 program [13, 16].

8. Sourcing and Quality Verification

Research-grade relamorelin is supplied by multiple peptide and pharmaceutical research suppliers including MedChemExpress, MedKoo Biosciences, Cayman Chemical, Selleckchem, BOC Sciences, Clearsynth, and TargetMol. The compound is available as the free base, the acetate salt, or the trifluoroacetate salt, at purities reported as greater than 95 to 98 percent by HPLC.

Supply is in milligram quantities (typically 1 to 50 mg vials) suitable for in vitro pharmacology, cellular assays, and small-animal in vivo studies. Pricing is moderate to high, in the range of \$100 to \$500 per milligram depending on supplier, quantity, and salt form.

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

- High-performance liquid chromatography area-percent purity (greater than 95 percent, ideally greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (791.0 plus or minus 0.5 for the protonated free base $[M+H]^+$, with appropriate adjustment for salt counterion mass)
- Peptide content determination (net peptide content by amino acid analysis or nitrogen quantification, as lyophilized peptides may contain residual water, salts, and counterions that reduce the actual peptide mass fraction)
- Residual solvent analysis (gas chromatography for common peptide synthesis solvents: dimethylformamide, acetonitrile, trifluoroacetic acid, dichloromethane)
- Endotoxin testing if the material is intended for in vivo administration in animal models

Pharmaceutical-grade relamorelin (clinical trial material) is not commercially available; the compound is not marketed in any jurisdiction. Investigators requiring GMP-grade material for clinical research would need to arrange custom synthesis through a GMP peptide manufacturing organization.

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. Given the peptide nature and the moderate to high cost per milligram, on-receipt analytical confirmation is appropriate for any investigation where dose-response precision or in vivo reproducibility is important.

9. Reconstitution and Handling

Relamorelin is supplied as a lyophilized powder and should be stored at minus 20 degrees Celsius for long-term storage or at 2 to 8 degrees Celsius for short-term storage (weeks to months). The lyophilized material is stable under these conditions for at least 12 to 24 months based on supplier specifications.

Reconstitution for in vitro use: Dissolve in sterile dimethyl sulfoxide (DMSO) to prepare a concentrated stock solution (typically 10 to 50 mM). Store aliquots at minus 20 degrees Celsius. Dilute into aqueous buffer (phosphate-buffered saline, cell culture medium) immediately before use. Final DMSO concentration in cell-based assays should not exceed 0.1 to 0.5 percent to avoid solvent cytotoxicity.

Reconstitution for in vivo use: Dissolve in sterile normal saline (0.9 percent sodium chloride) or bacteriostatic water for injection. Prepare fresh solutions for each experimental session or store reconstituted material at 2 to 8 degrees Celsius for no more than 7 to 14 days. Filter-sterilize (0.22 micrometer) if preparing solutions for subcutaneous or intraperitoneal injection in animal models.

Handling precautions: Standard peptide handling practices apply. Avoid repeated freeze-thaw cycles of reconstituted solutions (aliquot for single use). Minimize exposure to temperatures above 25 degrees Celsius. The compound is not known to be hazardous at research concentrations; standard laboratory personal protective equipment (gloves, lab coat, eye protection) is appropriate.

Stability considerations: Peptides in aqueous solution are subject to hydrolysis and aggregation over time. Reconstituted relamorelin solutions should be used within 14 days of preparation when stored at 2 to 8 degrees Celsius. For longer storage requirements, aliquot and store frozen at minus 20 degrees Celsius; limit freeze-thaw cycles to fewer than 5 to maintain potency.

10. Stack Interactions and Combinations

Relamorelin interacts with several drug classes through its pharmacodynamic effects on gastrointestinal motility and growth hormone secretion. Investigators conducting research with relamorelin should consider:

Antidiabetic agents: Acceleration of gastric emptying by relamorelin can alter the pharmacokinetics and pharmacodynamics of orally administered antidiabetic medications. Insulin-treated patients may experience hyperglycemia if insulin dosing is calibrated to the delayed gastric emptying rate of untreated gastroparesis. Sulfonylureas, DPP-4 inhibitors, and alpha-glucosidase inhibitors may require dose timing adjustment. GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide) delay gastric emptying through a distinct mechanism and may partially oppose the prokinetic effect of relamorelin [9, 22].

Opioid analgesics: Opioids delay gastric emptying through mu-receptor activation on enteric neurons. Relamorelin's prokinetic effect is partially or fully reversible in morphine-induced gastroparesis models. Concurrent opioid use may reduce the clinical efficacy of relamorelin, though the preclinical evidence demonstrates that relamorelin can overcome moderate opioid-induced gastroparesis [2, 5].

Motilin receptor agonists (erythromycin): The combination of a ghrelin receptor agonist and a motilin receptor agonist has theoretical additive or synergistic prokinetic potential but has not been characterized in clinical studies. Both mechanisms act on the enteric nervous system through distinct receptor pathways. The combination may increase the risk of abdominal cramping and diarrhea.

Dopamine receptor antagonists (metoclopramide, domperidone): These prokinetic agents act through antidopaminergic mechanisms in the enteric and central nervous systems. Combination with relamorelin would produce additive prokinetic effects through distinct mechanisms. No formal drug-drug interaction studies have been conducted.

Anticholinergic agents: Medications with anticholinergic properties (tricyclic antidepressants, antihistamines, antispasmodics) delay gastric emptying and may reduce the efficacy of relamorelin. Investigators should consider the net effect on gastric motility when combining relamorelin with anticholinergic medications in research protocols.

Growth hormone and IGF-1 pathway agents: Concurrent administration with exogenous growth hormone, growth hormone-releasing hormone analogs (tesamorelin), or other growth hormone secretagogues (ipamorelin, GHRP-6) would produce additive GH-axis stimulation. The combination is not anticipated in clinical gastroparesis treatment but may be relevant in research settings investigating growth hormone pharmacology or in contexts where both motility and anabolic effects are desired.

Somatostatin analogs (octreotide): Somatostatin analogs suppress growth hormone release and can inhibit gastrointestinal motility at higher doses while stimulating migrating motor complex activity at lower doses. The pharmacodynamic interaction with relamorelin is complex and dose-dependent; the combination has not been formally characterized.

Other ghrelin receptor agonists (ipamorelin, anamorelin, macimorelin): Concurrent administration with other GHSR-1a agonists would produce additive receptor activation. No clinical rationale exists for combining two ghrelin agonists, but investigators studying receptor pharmacology should consider the cumulative receptor occupancy and potential for desensitization.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed across Phase 2 clinical trials at therapeutic doses (10 to 100 micrograms subcutaneously once or twice daily) are:

- Hyperglycemia (dose-dependent; 14.5 percent of relamorelin-treated patients in Phase 2b; reflects accelerated nutrient delivery to absorptive small intestine)
- Diarrhea (dose-dependent; consistent with gastrocolokinetic mechanism)
- Headache (5 to 10 percent; similar to placebo rates in some studies)
- Dizziness (3 to 7 percent)
- Nausea (2 to 5 percent; paradoxical in a gastroparesis population; may reflect overly rapid gastric emptying)
- Abdominal pain (2 to 5 percent)

These adverse events are consistent with the pharmacological mechanism and are generally mild to moderate in severity [9, 10, 22].

11.2 Injection site reactions

No clinically significant injection site reactions have been reported across the Phase 1, 2a, and 2b clinical programs. Subcutaneous injection was well tolerated at all studied doses. This favorable local tolerability distinguishes relamorelin from some other subcutaneous peptide therapeutics that produce lipodystrophy, erythema, or induration at injection sites [22].

11.3 Growth hormone elevation

Relamorelin produces dose-dependent elevations in plasma growth hormone, prolactin, and cortisol as expected on-target pharmacodynamic effects of GHSR-1a activation. The clinical significance of chronic growth hormone elevation in the context of long-term gastroparesis treatment has not been fully characterized owing to the termination of the Phase 3 long-term safety extension. Potential concerns in-

clude effects on glucose metabolism (growth hormone is counterregulatory to insulin), fluid retention, and theoretical long-term effects on IGF-1-mediated cell proliferation. These concerns remain theoretical at the doses and durations studied in completed trials [2, 5, 22].

11.4 Hyperglycemia considerations

The hyperglycemia signal is the most clinically significant adverse finding and requires specific management consideration. In diabetic populations with gastroparesis, the baseline glycemic regimen is optimized for delayed gastric emptying. Restoration of normal or near-normal gastric emptying rates by relamorelin produces earlier and higher postprandial glucose excursions unless the antidiabetic regimen (particularly prandial insulin timing and dose) is adjusted concurrently. The Phase 2b study demonstrated a clear dose-response relationship for hyperglycemia events (3 placebo, 8 at 10 micrograms, 17 at 30 micrograms, 17 at 100 micrograms), supporting a mechanistic explanation rather than an idiosyncratic drug reaction [9, 22].

Management strategies include prospective adjustment of prandial insulin timing (administering insulin earlier relative to meal onset), reduction in prandial insulin dose with subsequent titration, and more frequent glycemic monitoring during the initial treatment period. These adjustments represent an expected clinical management consideration for any effective gastroparesis prokinetic in the diabetic population.

11.5 Pregnancy and lactation

No human pregnancy or lactation data are available. As a ghrelin receptor agonist with growth hormone-releasing activity, the compound would require reproductive toxicology characterization before use in pregnant or lactating populations. Preclinical reproductive and developmental toxicology data have not been published.

11.6 Long-term safety

Long-term safety data (beyond 12 weeks) are not available from completed clinical trials. The PLEDGE program included a long-term open-label safety extension designed to follow participants for up to 5 years on active treatment; this study was

terminated before completion. Investigators considering chronic administration in preclinical models should monitor for effects on glucose homeostasis, body composition, and growth hormone-axis feedback regulation.

11.7 Cardiovascular safety

No clinically significant cardiovascular adverse events, QT interval prolongation, or arrhythmias have been reported in the relamorelin clinical program. This favorable cardiovascular profile compares favorably to domperidone (QT prolongation risk) and cisapride (withdrawn for cardiac arrhythmia) in the prokinetic therapeutic class.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five therapeutic candidates for gastroparesis and gastrointestinal dysmotility against relamorelin, evaluated on five 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 prokinetic agents with substantive clinical pharmacology programs or established clinical use in gastroparesis, with priority on those sharing mechanistic relevance to relamorelin or representing the current standard of care.

12.1 Metoclopramide

Mechanism: Peripheral and central dopamine D2 receptor antagonist with additional 5-HT₄ receptor agonist and weak 5-HT₃ receptor antagonist activity. The prokinetic effect is mediated through both antidopaminergic disinhibition of enteric cholinergic neurons and direct 5-HT₄-mediated enhancement of acetylcholine release in the myenteric plexus.

Regulatory status: The only FDA-approved pharmacotherapy for gastroparesis (approved 1980). Approved for short-term use (up to 12 weeks) at 10 mg three times daily before meals. Carries a black-box warning for tardive dyskinesia risk with chronic use.

Novelty: Low. The compound has been available for over 40 years and represents the oldest prokinetic mechanism in clinical use.

Effect size: Moderate for symptom improvement. Meta-analyses demonstrate significant improvement in gastroparesis symptoms versus placebo, with efficacy declining over chronic use (tachyphylaxis). Gastric emptying acceleration is modest compared to relamorelin [23, 24].

Promising potential: Low for further development; the compound is generic and off-patent. High for continued clinical utility given its status as the only approved agent.

Side-effect profile: The principal safety concern is extrapyramidal symptoms, including the risk of irreversible tardive dyskinesia with prolonged administration (estimated at 1 to 10 percent), which prompted the FDA black-box warning. Additional adverse events include drowsiness, fatigue, depression, and hyperprolactinemia. The central nervous system penetration and dopamine antagonism produce a substantially less favorable safety profile than relamorelin for chronic use [23, 24].

Overall validation: High. Decades of clinical experience, large-scale meta-analyses, and regulatory approval establish metoclopramide as a validated but imperfect gastroparesis therapy.

Comparison to relamorelin: Relamorelin has a fundamentally different and more favorable safety profile (no tardive dyskinesia risk, no central dopamine antagonism), a larger effect on gastric emptying acceleration, and a specific mechanism (GHSR-1a agonism) designed for the pathophysiology of gastroparesis. Metoclopramide has the advantage of oral administration, regulatory approval, generic availability, and decades of clinical experience.

12.2 Domperidone

Mechanism: Peripheral dopamine D2 receptor antagonist with minimal blood-brain barrier penetration. Prokinetic effect is mediated through antidopaminergic disinhibition of enteric cholinergic neurons, similar to metoclopramide but without the central dopamine antagonism that produces extrapyramidal side effects.

Regulatory status: Available in many countries outside the United States (Europe, Canada, Asia, Latin America) for gastroparesis and nausea. Not FDA-approved in the United States; available only through FDA Expanded Access/Investigational New Drug programs.

Novelty: Low. The compound has been available for over 40 years and is mechanistically conventional.

Effect size: Moderate. Clinical trials demonstrate symptom improvement comparable to metoclopramide. Gastric emptying acceleration is modest [23, 24].

Promising potential: Low for further development; the compound is generic and its development pathway is largely complete.

Side-effect profile: More favorable than metoclopramide regarding central nervous system effects (minimal tardive dyskinesia risk). The principal safety concern is cardiac: domperidone has been associated with QT interval prolongation and ventricular arrhythmias, particularly at higher doses and in patients with pre-existing cardiac risk factors [23, 24].

Overall validation: High. Extensive worldwide clinical experience, regulatory approval in multiple jurisdictions, and established position in gastroparesis treatment guidelines.

Comparison to relamorelin: Relamorelin has no cardiac arrhythmia signal, a distinct mechanism without antidopaminergic activity, and larger gastric emptying acceleration effects. Domperidone has the advantage of oral administration and widespread global availability.

12.3 Prucalopride

Mechanism: Highly selective 5-HT₄ (serotonin type 4) receptor agonist. Activates 5-HT₄ receptors on enteric neurons to enhance acetylcholine release and stimulate intestinal motility, predominantly colonic but with some gastric prokinetic effect.

Regulatory status: FDA-approved for chronic idiopathic constipation (2018); EMA-approved for chronic constipation. Not approved for gastroparesis, though studied in this indication.

Novelty: Moderate. While 5-HT₄ agonism is an established prokinetic mechanism (cisapride, tegaserod), prucalopride's high selectivity for the 5-HT₄ receptor avoids the cardiac and other off-target effects that led to withdrawal of earlier agents in this class.

Effect size: In a randomized crossover study of 34 gastroparesis patients, prucalopride 2 mg daily for 4 weeks improved total Gastroparesis Cardinal Symptom Index compared to placebo. Effect sizes on gastric emptying are modest [24, 25].

Promising potential: Moderate. The compound is approved for constipation but not gastroparesis; off-label use in gastroparesis is increasing based on limited but positive clinical data.

Side-effect profile: Generally well tolerated. The principal adverse events are headache, diarrhea, and abdominal pain. No QT prolongation or cardiac safety signal at approved doses [24, 25].

Overall validation: Moderate for gastroparesis (limited data); high for chronic constipation (Phase 3 registration data and regulatory approval).

Comparison to relamorelin: Both have favorable safety profiles and act through novel mechanisms. Relamorelin has a larger clinical evidence base specifically in diabetic gastroparesis (approximately 600 patients versus a single small crossover study for prucalopride). Prucalopride has the advantage of oral administration and regulatory approval (for constipation).

12.4 Camicinal (GSK962040)

Mechanism: Small-molecule motilin receptor agonist. Activates the motilin receptor on enteric neurons and smooth muscle to stimulate phase III migrating motor complex contractions and accelerate gastric emptying, mimicking the prokinetic mechanism of erythromycin without the antibiotic activity.

Regulatory status: Investigational. Completed Phase 2 studies in gastroparesis and critical illness-associated gastroparesis. Not approved in any jurisdiction.

Novelty: Moderate. The motilin receptor agonist mechanism is established (erythromycin), but camicinal represents a non-antibiotic, selective motilin agonist without the tachyphylaxis that limits chronic erythromycin use.

Effect size: Phase 2 studies in critical illness-associated gastroparesis demonstrated acceleration of gastric emptying and improved enteral feed tolerance. Effect sizes in diabetic gastroparesis were modest. Network meta-analyses position camicinal with a relatively favorable safety profile [24, 26].

Promising potential: Low to moderate. Development by GlaxoSmithKline appears to have been deprioritized following mixed Phase 2 results. The compound is not in active late-stage development.

Side-effect profile: Generally well tolerated in Phase 2 studies. Lower rates of withdrawal due to adverse events compared to several comparator prokinetic agents [24, 26].

Overall validation: Low to moderate. Phase 2 data available but no Phase 3 registration program completed or initiated.

Comparison to relamorelin: Both are investigational prokinetic agents acting through distinct receptor mechanisms (ghrelin versus motilin). Relamorelin has a substantially larger clinical evidence base and a broader gastrocolokinetic profile (gastric plus colonic versus predominantly gastric for motilin agonism). Camicinal has the advantage of oral administration. Neither compound is approved.

12.5 Tradipitant (VLY-686)

Mechanism: Selective neurokinin-1 (NK1) receptor antagonist. Blocks substance P signaling at NK1 receptors in the central nervous system and gastrointestinal tract, reducing nausea and potentially modulating gastric motility through the enteric nervous system.

Regulatory status: Investigational. Completed Phase 3 trials in gastroparesis (Vanda Pharmaceuticals). FDA New Drug Application submitted for gastroparesis indication.

Novelty: High. The NK1 receptor antagonist mechanism is novel for gastroparesis treatment. While NK1 antagonists are established as antiemetics for chemotherapy-induced nausea (aprepitant), their development specifically for gastroparesis symptom relief represents a new therapeutic concept.

Effect size: Phase 3 studies reported significant improvement in gastroparesis symptoms (nausea, vomiting, early satiety) compared to placebo. The mechanism addresses symptom perception rather than gastric motility, representing a fundamentally different therapeutic strategy from relamorelin [24].

Promising potential: High. Active NDA submission and potential for regulatory approval would establish a new mechanism-based therapy for gastroparesis.

Side-effect profile: Generally well tolerated in Phase 3 studies. The NK1 antagonist mechanism has an established safety profile from the oncology antiemetic class.

Overall validation: Moderate to high. Phase 3 data supporting efficacy in gastroparesis, with regulatory review underway.

Comparison to relamorelin: Tradipitant and relamorelin represent fundamentally different therapeutic strategies. Relamorelin targets the underlying motility deficit (delayed gastric emptying) through GHSR-1a agonism, while tradipitant targets symptom perception (nausea and vomiting) through NK1 antagonism without necessarily accelerating gastric emptying. The two mechanisms could theoretically be complementary. Tradipitant has the advantage of oral administration and advanced regulatory status.

12.6 Comparator summary

The five compounds occupy distinct positions in the gastroparesis therapeutic landscape. **Metoclopramide** is the regulatory gold standard but is limited by tardive dyskinesia risk and is unsuitable for chronic use. **Domperidone** provides similar efficacy with a better central nervous system safety profile but carries cardiac arrhythmia risk. **Prucalopride** offers a safe oral prokinetic with modest gastroparesis evidence but established constipation approval. **Camicinal** represents a motilin receptor approach with limited development progress. **Tradipitant** introduces a novel symptom-targeting mechanism with advanced regulatory status.

Relamorelin occupies a unique position as the only ghrelin receptor agonist to reach Phase 3 development for gastroparesis, with the largest clinical evidence base specifically in diabetic gastroparesis of any investigational prokinetic, and with a mechanism that directly addresses the gastric emptying delay that defines the condition. The gastrocolokinetic profile (gastric plus colonic effects) provides additional therapeutic potential for constipation-predominant presentations. The principal limitations are the requirement for subcutaneous administration, the hyperglycemia signal in diabetic populations, and the absence of regulatory approval following program termination. The termination appears to reflect corporate portfolio decisions rather than fundamental pharmacological or safety limitations, and the clinical evidence base supports the continued scientific rationale for ghrelin receptor agonism in gastrointestinal dysmotility.

13. References

1. Van Craenenbroeck M, Gregoire F, De Neef P, et al. Agonistic properties of BIM-28131, a novel synthetic pentapeptide ghrelin analog. *Endocrine Abstracts*. 2004.
2. Shin A, Camilleri M, Busciglio I, et al. Emerging treatments in neurogastroenterology: relamorelin: a novel gastrocolokinetic synthetic ghrelin agonist. *Neurogastroenterol Motil*. 2015;27(3):324-332.
3. Ipsen. Patent applications relating to synthetic ghrelin receptor agonist pentapeptides (BIM-28131 series). International patent filings WO/2004/056866 and related applications.
4. MedChemExpress. Relamorelin (RM-131) product specification sheet. CAS 661472-41-9.
5. Camilleri M, Acosta A. Emerging treatments in neurogastroenterology: relamorelin: a novel gastrocolokinetic synthetic ghrelin agonist. *Neurogastroenterol Motil*. 2015;27(3):324-332.
6. Camilleri M. Gastroparesis: etiology, clinical manifestations, and diagnosis. *UpToDate/Gastroenterology Reviews*. 2019.
7. Sanger GJ, Furness JB. Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol*. 2016;13(1):38-48.
8. Shin A, Camilleri M, Busciglio I, et al. Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis. *Gastroenterology*. 2016;151(1):87-96.e6.
9. Camilleri M, McCallum RW, Tack J, et al. Efficacy and safety of relamorelin in diabetics with symptoms of gastroparesis: a randomized, placebo-controlled study. *Gastroenterology*. 2017;153(5):1240-1250.e2.
10. Lembo A, Camilleri M, McCallum R, et al. Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis. *Gastroenterology*. 2016;150(4):S527.

11. Acosta A, Camilleri M, Kolar G, et al. Relamorelin relieves constipation and accelerates colonic transit in a phase 2, placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol*. 2015;13(13):2312-2319.e1.
12. Fazeli PK, Calder GL, Miller KK, et al. Treatment with a ghrelin agonist in outpatient women with anorexia nervosa: a randomized clinical trial. *J Clin Psychiatry*. 2018;79(1):17m11585.
13. Allergan/AbbVie. Allergan expands PLEDGE clinical research program in diabetic gastroparesis. Press release, May 17, 2019.
14. Rhythm Pharmaceuticals. SEC Form S-1 filing. 2014.
15. Allergan. Allergan acquires Motus Therapeutics and relamorelin program. Press release, 2016.
16. ClinicalTrials.gov. Study to evaluate the safety and efficacy of relamorelin in diabetic gastroparesis (RLM-MD-01). NCT03426345. Status: Terminated.
17. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*. 1999;402(6762):656-660.
18. Howard AD, Feighner SD, Cully DF, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science*. 1996;273(5277):974-977.
19. Nelson AD, Camilleri M, Acosta A, et al. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. *Neurogastroenterol Motil*. 2016;28(11):1705-1713.
20. Acosta A, Camilleri M, Busciglio I, et al. Short-term effects of relamorelin on descending colon motility in chronic constipation: a randomized, controlled trial. *Dig Dis Sci*. 2016;61(3):852-860.
21. Ishida J, Saitoh M, Ebner N, et al. Growth hormone secretagogues: history, mechanism of action, and clinical development. *JCSM Rapid Commun*. 2020;3(1):25-37.
22. Acosta A, Camilleri M, Shin A, et al. Overall safety of relamorelin in adults with diabetic gastroparesis: analysis of phase 2a and 2b trial data. *Aliment Pharmacol Ther*. 2020;51(12):1227-1238.
23. Camilleri M. Gastroparesis: current concepts and future directions. *Gastroenterology*. 2022;162(1):68-87.

24. Schol J, Huang IH,"; et al. Efficacy and safety of drugs for gastroparesis: systematic review and network meta-analysis. *Gastroenterology*. 2023;164(4):642-654.
25. Carbone F, Van den Houte K, Clevers E, et al. Prucalopride in gastroparesis: a randomized placebo-controlled crossover study. *Am J Gastroenterol*. 2019;114(8):1265-1274.
26. Chapman MJ, Deane AM, O'Connor SL, et al. The effect of camicinal (GSK962040), a motilin agonist, on gastric emptying in critically ill patients. *Crit Care*. 2016;20(1):232.
27. Thorner MO, Perez-Tilve D, Tschop MH. Ghrelin receptor (GHSR) agonists for treatment of metabolic and gastrointestinal disorders. *Expert Opin Investig Drugs*. 2017;26(10):1163-1174.
28. Ali T, Hasan M, Hamadani M, et al. Gastroparesis. *South Med J*. 2019;112(4):197-205.
29. Singh R, Zogg H, Bhagwate A, et al. Current treatment options and therapeutic insights for gastrointestinal dysmotility and functional gastrointestinal disorders. *Front Pharmacol*. 2022;13:808195.
30. Wo JM, Nowak TV, Waseem S, et al. Gastroparesis drug development: progress and challenges. *Gastroenterology*. 2020;159(3):812-816.

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