

RESEARCH MONOGRAPH . COMPOUND PROFILE

Macimorelin

An orally active peptidomimetic ghrelin receptor agonist developed at the University of Montpellier and advanced by Aeterna Zentaris as the first and only approved oral diagnostic test for adult growth hormone deficiency, distinguished from other growth hormone secretagogues by its validated diagnostic application and favorable safety profile relative to the insulin tolerance test.

DOCUMENT	KDC-MN-1419
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Synthetic peptidomimetic growth hormone secretagogue receptor type 1a (GHS-R1a) agonist

ABSTRACT

Macimorelin (JMV-1843, EP-1572, AEZS-130), a synthetic peptidomimetic agonist of the growth hormone secretagogue receptor type 1a (GHS-R1a, the ghrelin receptor), is the first and only orally administered diagnostic agent approved by the United States Food and Drug Administration (December 2017) and the European Medicines Agency (January 2019) for the evaluation of adult growth hormone deficiency (AGHD). The compound was invented and first synthesized at the University of Montpellier and the Centre National de la Recherche Scientifique (CNRS) in France by Fehrentz, Martinez, Guerlavis, and colleagues as part of a structure-activity program seeking orally bioavailable growth hormone secretagogues derived from the hexarelin scaffold, and was subsequently licensed to Aeterna Zentaris for clinical development and marketed under the trade names Macrilen (United States, Novo Nordisk) and Ghryvelin (European Union, Consilient Health and subsequently Pharmanovia) [1, 2]. Structurally, macimorelin is a modified tripeptide containing two indole (tryptophan-derived) moieties linked through a central peptidomimetic backbone with a terminal formamide group and an N-terminal alpha-aminoisobutyric acid cap, conferring oral bioavailability and resistance to proteolytic degradation that distinguish it from the earlier peptide-based growth hormone secretagogues such as GHRP-6 and hexarelin.

The compound binds the GHS-R1a receptor on pituitary somatotroph cells with an IC₅₀ of 22.9 nanomolar in human pituitary tissue and activates the Gq/11-phospholipase C signaling cascade, stimulating endogenous growth hormone release into the

systemic circulation in a manner pharmacologically analogous to the endogenous ligand ghrelin [2, 3]. Following oral administration at the diagnostic dose of 0.5 mg/kg body weight, macimorelin produces a robust and reproducible rise in serum growth hormone concentration that peaks between 30 and 90 minutes post-dose, permitting diagnostic discrimination between growth hormone-sufficient and growth hormone-deficient adults through serial blood sampling over a 90-minute test window. The Phase 3 confirmatory trial (Garcia et al., 2018) in 157 adults demonstrated 87 percent sensitivity and 96 percent specificity at a growth hormone cutoff of 2.8 ng/mL, with 97 percent reproducibility on repeat testing, establishing macimorelin as a clinically validated alternative to the insulin tolerance test with the practical advantages of oral administration, absence of hypoglycemia risk, and a shorter, simpler test protocol [4, 5].

Pharmacokinetics are characterized by rapid oral absorption (median time to peak plasma concentration approximately 0.75 hours), hepatic metabolism predominantly through cytochrome P450 3A4 (CYP3A4) to a partially active O-demethylated metabolite, a terminal elimination half-life of approximately 4.1 hours, approximately 70 percent plasma protein binding, and predominantly fecal excretion [6, 7]. Food substantially reduces both the rate and extent of absorption (C_{max} reduction of approximately 55 percent, AUC reduction of approximately 44 to 49 percent with a high-fat meal), mandating overnight fasting before the diagnostic test. The principal drug interaction concern is with strong CYP3A4 inducers (which may reduce macimorelin exposure and produce false-positive diagnostic results) and strong CYP3A4 inhibitors (which may elevate exposure). The compound produces a mean increase in the corrected QT interval of approximately 11 milliseconds at the diagnostic dose, requiring

avoidance of concomitant QT-prolonging medications during the test [8].

Adverse events in clinical trials were mild and transient, with dysgeusia (bitter or metallic taste), dizziness, headache, nausea, fatigue, hunger, and diarrhea reported at low frequencies. No serious adverse events attributable to macimorelin were reported in the pivotal trials across more than 1000 administered subjects [5, 8]. The compound is administered as a single diagnostic dose rather than as a chronic therapeutic regimen, and the safety profile reflects this acute exposure context. Beyond the diagnostic indication, macimorelin has been investigated in cancer cachexia (pilot trial demonstrating safety and numerical weight improvement) and in pharmaco-resistant epilepsy (preclinical seizure suppression through GHS-R1a-mediated neuroprotection), though the compound is not approved for any therapeutic application [9, 10].

This monograph reviews the chemistry, synthesis, and structural pharmacology of macimorelin; the GHS-R1a receptor mechanism in molecular detail; the comprehensive human pharmacokinetic record; the preclinical and clinical evidence base across diagnostic and investigational applications; reconstitution and handling considerations; stack interactions and drug-drug interaction considerations; the adverse-event and safety signal; and a comparative assessment of five growth hormone secretagogue or diagnostic candidates (insulin tolerance test, glucagon stimulation test, anamorelin, ibutamoren, and GHRH-arginine test) against macimorelin on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Macimorelin.

Marketed names: Macrilen (Novo Nordisk; United States), Ghryvelin (Consilient Health, subsequently Pharmanovia; European Union, United Kingdom).

Development codes: JMV-1843 (University of Montpellier/CNRS original designation), EP-1572 (Europeptides designation), AEZS-130 (Aeterna Zentaris clinical development code), ARD-07 (Ardana Biosciences designation). The JMV-1843 designation is the canonical identifier in the original medicinal chemistry literature from the Fehrentz and Martinez laboratory [1, 2].

Chemical Abstracts Service registry numbers: 381231-18-1 (free base), 945212-59-9 (acetate salt). The acetate salt is the formulated pharmaceutical material; the free base is the synthetic and analytical reference form.

International Union of Pure and Applied Chemistry name: 2-Methylalanyl-N-[(1R)-1-formamido-2-(1H-indol-3-yl)ethyl]-D-tryptophanamide. The compound is a peptidomimetic tripeptide analog incorporating two D-tryptophan-derived indolyl-methyl groups connected through a central amide backbone with a terminal formamide and an N-terminal alpha-aminoisobutyric acid residue [2].

1.2 Structural class and chemistry

Macimorelin is a peptidomimetic growth hormone secretagogue belonging to the modified tripeptide class of ghrelin receptor agonists. The structural class places it between the early peptide-based secretagogues (GHRP-6, hexarelin, ipamorelin) and the fully non-peptide small molecules (ibutamoren/MK-677) in the medicinal chemistry evolution of GHS-R1a ligands [2, 11].

Molecular formula: C₂₆H₃₀N₆O₃ (free base); C₂₈H₃₄N₆O₅ (acetate salt).

Exact mass: 474.2379 g/mol (free base, monoisotopic).

Molecular weight: 474.57 g/mol (free base); 534.62 g/mol (acetate salt).

Physical properties: White to off-white powder. Freely soluble in water (as the acetate salt), soluble in dimethyl sulfoxide, methanol, and ethanol; sparingly soluble in apolar organic solvents. The compound is supplied as the acetate salt for pharmaceutical use and is reconstituted as an oral solution immediately prior to administration.

Stereochemistry: Macimorelin contains one defined stereocenter at the C-terminal diaminoindolylethyl carbon (R-configuration) and the D-configuration at the central tryptophan residue. The alpha-aminoisobutyric acid residue is achiral (gem-dimethyl substitution). The stereochemical configuration is critical for receptor binding; the corresponding L-tryptophan and S-configured analogs show substantially reduced GHS-R1a affinity in the published structure-activity relationship [2].

1.3 Synthesis

The published synthesis of macimorelin (JMV-1843) proceeds from the Guerlavais et al. (2003) medicinal chemistry program at the University of Montpellier [2]. The synthetic route employs standard peptide coupling chemistry with modifications for the non-natural residues. The N-terminal alpha-aminoisobutyric acid is coupled to D-tryptophan using carbodiimide or uronium-mediated amide bond formation (HBTU, HATU, or EDC/HOBt). The resulting dipeptide is then coupled to the C-terminal (R)-1-formamido-2-(1H-indol-3-yl)ethylamine fragment. The C-terminal fragment is itself prepared from D-tryptophan through reductive amination and formylation steps. The final product is purified by preparative high-performance liquid chromatography and converted to the acetate salt by lyophilization from acetic acid solution [1, 2].

The key design principles that distinguish macimorelin from earlier growth hormone secretagogue peptides include: incorporation of alpha-aminoisobutyric acid to confer proteolytic resistance; use of D-tryptophan to further resist peptidase degradation; reduction of the peptide backbone to three residues to minimize molecular weight and hydrogen bond donors for oral absorption; and the gem-diamino C-terminal pharmacophore that engages the GHS-R1a binding pocket [2]. The compound was selected from a series of approximately 30 analogs on the basis of combined oral bioavailability in beagle dogs, binding affinity to the human pituitary GHS receptor, and in vivo growth hormone releasing potency in rats exceed-

ing that of the reference compound hexarelin [2]. Industrial synthesis for pharmaceutical supply employs optimized versions of this route with yields reported in the range of 40 to 60 percent overall from commercial amino acid starting materials.

2. Abstract

Macimorelin (AEZS-130, JMV-1843, EP-1572) is a synthetic, orally bioavailable peptidomimetic agonist of the growth hormone secretagogue receptor type 1a (GHS-R1a), approved by the United States Food and Drug Administration (December 2017) and the European Medicines Agency (2019) as the first oral diagnostic test for adult growth hormone deficiency (AGHD) [4, 5]. The compound stimulates pituitary growth hormone release through activation of the ghrelin receptor signaling cascade and is administered as a single oral dose of 0.5 mg/kg body weight, with serum growth hormone measurements at baseline and at 30, 45, and 90 minutes post-dose to determine whether the growth hormone response exceeds the diagnostic cutoff of 2.8 ng/mL [5, 8].

The diagnostic indication addresses a longstanding clinical need. Prior to macimorelin, the gold standard test for AGHD was the insulin tolerance test (ITT), which requires induction of symptomatic hypoglycemia through intravenous insulin administration, continuous medical supervision, and is contraindicated in patients with seizure disorders, coronary artery disease, and cerebrovascular disease [12]. The GHRH-arginine test, a validated alternative, became unavailable in the United States following withdrawal of synthetic GHRH from the market in 2008 [13]. The glucagon stimulation test, while available, requires intramuscular injection and 3 to 4 hours of monitoring with substantial nausea and vomiting [12]. Macimorelin provides a simple, well-tolerated oral test requiring 90 minutes, four blood draws, and no induction of hypoglycemia, with diagnostic accuracy comparable to the ITT.

The pivotal Phase 3 trial (Garcia et al. 2018) enrolled 157 subjects across high-likelihood, intermediate-likelihood, and low-likelihood AGHD groups in an open-label, randomized, two-way crossover design comparing the macimorelin growth hormone stimulation test with the ITT [5]. At a growth hormone cutoff of 2.8 ng/mL, estimated sensitivity was 87 percent and specificity was 96 percent. Negative agreement with the ITT was 95.4 percent and positive agreement was 74.3 percent. Reproducibility on repeat testing was 97 percent, substantially exceeding the reported reproducibility of the ITT (approximately 90 percent) and the glucagon stimulation test [5]. Earlier Phase 2 validation (Garcia et al. 2013) in 48 AGHD patients and 50 matched controls demonstrated comparable accuracy to the GHRH-arginine test [4].

Beyond the diagnostic application, macimorelin has been investigated in cancer cachexia (Herodes et al. 2023; pilot randomized placebo-controlled trial demonstrating safety and numerical weight gain over one week of daily dosing) [9] and in pharmaco-resistant temporal lobe epilepsy (Clynen et al. 2021; significant seizure suppression in the intrahippocampal kainic acid mouse model) [10]. A pediatric development program is in progress, with a Phase 2 dose-escalation study (Allas et al. 2021) demonstrating safety and dose-dependent growth hormone release in children aged 2 to 17 years [14], and a Phase 3 trial comparing macimorelin to clonidine and arginine stimulation tests ongoing [15].

Pharmacokinetics in adults are characterized by rapid oral absorption (T_{max} 0.5 to 0.75 hours), hepatic CYP3A4-mediated O-demethylation to a partially active metabolite, terminal elimination half-life of approximately 4.1 hours, and predominantly fecal excretion [6, 7]. Drug interactions are principally through CYP3A4 modulation: strong inhibitors increase macimorelin exposure and may potentiate the growth hormone response, while strong inducers decrease exposure and may produce false-positive diagnostic results [8].

The compound is well tolerated. Across more than 1000 subjects administered macimorelin in clinical studies, no serious adverse events attributable to the compound have been reported [5, 8]. The principal adverse events are dysgeusia (transient bitter/metallic taste, approximately 9 percent), headache (approximately 6 percent), dizziness, fatigue, and nausea, all mild and self-limiting. The QTc prolongation of approximately 11 milliseconds at the diagnostic dose requires avoidance of concomitant QT-prolonging medications [8].

This monograph documents the chemistry, synthesis, and structure-activity relationships; the molecular pharmacology of GHS-R1a activation; the comprehensive human pharmacokinetic record; the preclinical and clinical evidence across diagnostic, cachexia, epilepsy, and pediatric applications; sourcing and quality verification; reconstitution and handling; stack interactions; adverse-event signal; and a comparative assessment of five growth hormone secretagogue or diagnostic candidates against macimorelin on five standards.

3. Discovery and Development History

3.1 Origin

Macimorelin was invented at the Laboratoire des Amino Acides, Peptides et Proteines (LAPP) at the University of Montpellier and the Centre National de la Recherche Scientifique (CNRS) in Montpellier, France, during the late 1990s. The compound emerged from a structure-activity program led by Jean-Alain Fehrentz, Jean Martinez, and Vincent Guerlavais that systematically truncated and modified peptidic growth hormone secretagogues derived from the hexapeptide GHRP-6 series [1, 2]. The discovery program was conducted in collaboration with Romano Deghenghi at Europeptides (France) and with academic groups at the Universities of Milano and Torino (Italy), and was motivated by the clinical limitation of the earlier generation of injectable growth hormone secretagogue peptides (GHRP-6, GHRP-2, hexarelin, ipamorelin) and the desire to create an orally bioavailable small-molecule or peptidomimetic analog suitable for chronic administration.

3.2 Medicinal chemistry rationale

The Guerlavais et al. (2003) publication described the systematic derivation of JMV-1843 from the lead compound EP-51389 [2]. The design strategy employed three principal modifications to achieve oral bioavailability: (a) incorporation of alpha-aminoisobutyric acid as the N-terminal residue to confer resistance to aminopeptidases; (b) use of D-configured tryptophan to resist endopeptidases; and (c) a gem-diamino C-terminal fragment (the formylated diaminoindolylethyl moiety) that functions as a reduced peptide bond isostere while maintaining the aromatic and hydrogen-bond donor pharmacophore required for GHS-R1a engagement [2]. The compound showed high oral bioavailability in beagle dogs, binding affinity to human pituitary GHS receptors with IC₅₀ of 22.9 nanomolar, and in vivo growth hormone releasing potency exceeding that of hexarelin in rats following oral administration [2].

3.3 Early clinical development

Phase 1 studies in healthy volunteers demonstrated that macimorelin, administered orally and by intraduodenal infusion, produced dose-dependent increases in serum growth hormone concentrations, with growth hormone levels remaining elevated for approximately 120 minutes after oral administration [16]. The growth hormone response was selective: cortisol, prolactin, and other anterior pituitary hormone levels were not significantly affected at growth hormone-stimulating doses, distinguishing macimorelin from less selective secretagogues. These Phase 1 data established the pharmacokinetic and pharmacodynamic basis for development as a diagnostic agent.

3.4 Licensing and corporate development

The compound was licensed from CNRS and the University of Montpellier to Ardana Biosciences Ltd. (Edinburgh, United Kingdom) for clinical development under the designation EP-1572. Ardana initiated the Phase 3 clinical trial program in the United States; however, the trial was suspended before completion because of Ardana's insolvency in 2008. Aeterna Zentaris (headquartered in Summerville, South Carolina) subsequently acquired all rights and clinical assets related to macimorelin through the insolvency process, reactivated the IND in 2009, and designated the compound AEZS-130 [8]. Aeterna Zentaris repositioned macimorelin as a diagnostic agent for AGHD rather than as a chronic therapeutic, a strategic decision driven by the substantially shorter and less expensive regulatory pathway for a single-dose diagnostic versus a chronic therapeutic compound, and by the clear unmet medical need created by the withdrawal of GHRH from the United States market in 2008.

3.5 Pivotal clinical trials and regulatory approval

Aeterna Zentaris completed the Phase 2 multicenter validation study comparing macimorelin to the GHRH plus arginine test (Garcia et al., 2013) and the Phase 3 confirmatory crossover trial comparing macimorelin to the insulin tolerance test (Garcia et al., 2018), both led by Jose M. Garcia at the VA Puget Sound Health Care System and the University of Washington [4, 5]. The FDA granted priority review designation and approved macimorelin (trade name Macrilen) on December 20,

2017, as the first oral diagnostic test for AGHD [17]. The European Medicines Agency granted marketing authorization in January 2019 under the name Ghryvelin (subsequently harmonized to Macrilen) [18].

3.6 Post-approval commercial history

In November 2018, Novo Nordisk acquired the United States commercial rights to Macrilen for \$145 million in upfront and milestone payments plus royalties on net sales. In November 2020, Aeterna Zentaris amended the license agreement with Novo Nordisk with modified terms. Novo Nordisk subsequently returned certain rights to Aeterna Zentaris in 2022 [19]. In Europe, Aeterna Zentaris licensed commercial rights to Consilient Health Ltd. (Dublin, Ireland) in December 2020, with Consilient launching the product under the trade name Ghryvelin in May 2022. Pharmanovia acquired the European marketing rights from Consilient Health in March 2023 [20]. Commercial availability in the United States has been intermittently disrupted; the product has experienced periods of limited supply while the manufacturer has worked to establish stable commercial partnerships.

3.7 Pediatric development

The pediatric development program was initiated with a Phase 2 open-label dose-escalation study (Allas et al., 2021) in children aged 2 to 17 years with suspected growth hormone deficiency, testing doses of 0.25, 0.5, and 1.0 mg/kg [14]. Results supported the 1.0 mg/kg dose for Phase 3 evaluation. A Phase 3 multicenter trial (NCT04786873) comparing macimorelin to clonidine and arginine stimulation tests in children with suspected growth hormone deficiency is ongoing and, if successful, would make macimorelin the first growth hormone stimulation test for pediatric patients to be approved on the basis of a randomized controlled trial [15].

4. Mechanism of Action

4.1 The growth hormone secretagogue receptor (GHS-R1a)

The growth hormone secretagogue receptor type 1a (GHS-R1a), also known as the ghrelin receptor, is a seven-transmembrane G protein-coupled receptor of the rhodopsin-like (Class A) family, encoded by the GHSR gene on human chromosome 3q26.31 and expressed predominantly on pituitary somatotroph cells, hypothalamic arcuate nucleus neurons, and at lower density on hippocampal neurons, vagal afferents, and peripheral immune cells [21]. The receptor is the cognate target of the endogenous 28-amino-acid acylated peptide hormone ghrelin (produced principally by gastric oxyntic cells) and mediates growth hormone release, appetite stimulation, energy homeostasis regulation, and neuroprotective signaling [21, 22].

GHS-R1a signals predominantly through the Gq/11 pathway: receptor activation stimulates phospholipase C beta (PLC-beta), generating inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate. IP3 mobilizes calcium from endoplasmic reticulum stores, and the resulting intracellular calcium elevation triggers growth hormone vesicle exocytosis from somatotroph cells. DAG activates protein kinase C, which contributes to sustained growth hormone secretion and to downstream gene expression effects [21, 22]. Secondary signaling through the ERK1/2 mitogen-activated protein kinase pathway and through beta-arrestin recruitment contributes to longer-term cellular responses including receptor internalization [22].

A distinguishing feature of GHS-R1a is high constitutive activity: approximately 50 percent of maximal signaling occurs in the absence of agonist, mediated by constitutive coupling to Gq/11 [23]. This constitutive activity has physiological relevance in maintaining basal growth hormone pulsatility and has pharmacological relevance in that inverse agonists (compounds that suppress constitutive activity below baseline) produce distinct effects from neutral antagonists.

4.2 Macimorelin receptor pharmacology

Macimorelin binds the human GHS-R1a receptor with high affinity. The IC₅₀ for displacement of radiolabeled ghrelin from human pituitary GHS receptor extracts is 22.9 nanomolar, and the IC₅₀ for the cloned human GHS-R1a receptor transiently expressed in LLC-PK1 cells is 123 nanomolar [2, 3]. The difference between these values likely reflects receptor reserve and coupling efficiency differences between native pituitary tissue (high receptor density, efficient coupling) and heterologous expression systems.

Functionally, macimorelin acts as a full agonist at GHS-R1a in calcium mobilization assays, producing dose-dependent intracellular calcium elevation with potency comparable to the endogenous ligand ghrelin [3]. The maximum efficacy (E_{max}) approaches that of ghrelin in somatotroph-derived cell lines, confirming full agonist classification rather than partial agonist behavior [3].

The selectivity of macimorelin for GHS-R1a over other G protein-coupled receptors has been characterized in broad-panel screening. The compound does not show significant activity (IC₅₀ greater than 10 micromolar) at dopamine receptors (D1 through D5), serotonin receptors (5-HT1 through 5-HT7), adrenergic receptors, muscarinic receptors, or opioid receptors at concentrations relevant to the diagnostic application [3, 8].

4.3 Structural basis of receptor binding

Recent cryo-electron microscopy studies have determined the structure of the GHS-R1a receptor bound to macimorelin at 2.63 angstrom resolution, providing atomic-level detail of the binding interaction [24]. Macimorelin occupies a bifurcated binding pocket within the transmembrane helical bundle, a pocket that is divided by a conserved salt bridge between glutamate 124 (position 3.33 in Ballesteros-Weinstein numbering) and arginine 283 (position 6.55). The two indole (tryptophan-derived) groups of macimorelin insert into the two lobes of this bifurcated pocket, with one indole engaging hydrophobic contacts with transmembrane helices 3 and 5 and the other indole engaging contacts with transmembrane helices 6 and 7. The formamide group at the C-terminus of macimorelin forms a hydrogen bond with a backbone carbonyl in the receptor extracellular loop 2, contributing to binding affinity and to the positioning of the molecule within the pocket [24]. Systematic mutagenesis and functional studies have identified the key residues underlying the

binding affinity of macimorelin and have shown that the binding mode is partially overlapping but not identical to that of anamorelin, explaining the pharmacokinetic and pharmacodynamic differences between the two compounds [24].

4.4 Growth hormone release mechanism

The physiological consequence of GHS-R1a activation on somatotroph cells is the release of stored growth hormone into the systemic circulation. The mechanism involves agonist binding producing Gq/11-coupled PLC-beta activation; PLC-beta generating IP3 and DAG from membrane PIP2; IP3 opening IP3-gated calcium channels on the endoplasmic reticulum, producing a rapid rise in cytoplasmic calcium; the calcium transient triggering exocytosis of growth hormone-containing secretory granules; and DAG-activated protein kinase C sustaining the secretory response and activating transcriptional programs that replenish growth hormone stores [21, 22].

The growth hormone release is synergistic with endogenous growth hormone-releasing hormone (GHRH) signaling. GHRH, released from hypothalamic arcuate nucleus neurons, activates the GHRH receptor (a Gs-coupled receptor) on somatotrophs, increasing cyclic AMP and activating protein kinase A. The GHS-R1a calcium signal and the GHRH receptor cyclic AMP signal converge at the level of exocytic machinery, producing a synergistic growth hormone release that exceeds the sum of the individual stimuli [22]. This synergy is the pharmacological basis for the robust growth hormone response to macimorelin even at moderate receptor occupancy.

4.5 Selectivity and ancillary effects

Macimorelin is selective for the GHS-R1a receptor relative to other G protein-coupled receptors involved in anterior pituitary hormone secretion. At growth hormone-stimulating doses, the compound does not produce clinically significant changes in cortisol, prolactin, thyroid-stimulating hormone, luteinizing hormone, or follicle-stimulating hormone concentrations, distinguishing it from less selective stimuli such as insulin-induced hypoglycemia (which activates the hypothalamic-pituitary-adrenal axis) and from GHRP-6 (which produces modest cortisol and prolactin elevation at higher doses) [4, 5, 16].

The GHS-R1a receptor is also expressed on hypothalamic neurons involved in appetite regulation, on vagal afferent neurons involved in gastrointestinal motility, and on several peripheral tissues. At the single diagnostic dose of macimorelin, these ancillary receptor populations produce mild, transient effects including hunger (reflecting hypothalamic appetite circuit activation) and mild gastrointestinal symptoms. These effects are pharmacologically expected and clinically insignificant in the diagnostic context.

4.6 Neuroprotective mechanisms

Preclinical work has characterized GHS-R1a activation as neuroprotective through multiple downstream pathways [10, 25]. Ghrelin receptor agonism activates extracellular signal-regulated kinase (ERK1/2) and phosphatidylinositol 3-kinase/Akt signaling in hippocampal neurons, reduces mitochondrial cytochrome c release, inhibits caspase-3 activation, and increases the Bcl-2/Bax ratio favoring neuronal survival [25]. Additionally, GHS-R1a activation suppresses microglial activation and reduces proinflammatory cytokine release (tumor necrosis factor alpha, interleukin-1 beta) in the hippocampus following excitotoxic challenge [10]. These mechanisms underlie the anticonvulsant and neuroprotective effects observed in seizure models.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Macimorelin is administered orally as a solution (the acetate salt dissolved in water). Absorption from the gastrointestinal tract is rapid, with time to maximum plasma concentration (T_{max}) of 0.5 to 0.75 hours in healthy adults at the 0.5 mg/kg diagnostic dose [6, 7]. The rapid absorption is consistent with the compound's moderate molecular weight (474 Da), limited hydrogen bond donors, and design optimization for oral bioavailability.

In the Phase 1 single-dose randomized controlled study (Piccoli et al., 2020), mean C_{max} values were dose-proportional across the 0.5, 1.0, and 2.0 mg/kg dose range [7]. At the approved diagnostic dose of 0.5 mg/kg, peak plasma concentrations are achieved within 30 to 45 minutes, coinciding with the timing of the growth hormone secretory response.

Food has a substantial negative effect on macimorelin absorption. Administration with a high-fat meal reduces C_{max} by approximately 55 percent and area under the concentration-time curve (AUC) by approximately 44 to 49 percent [8]. The reduced drug exposure can blunt the growth hormone response and produce false-positive diagnostic results. For this reason, the prescribing label mandates a minimum 8-hour overnight fast before the macimorelin test. Patients must also avoid strenuous physical exercise for 24 hours before the test, as exercise-induced growth hormone release can confound the diagnostic interpretation [8].

5.2 Distribution

Macimorelin has an apparent volume of distribution of approximately 4 liters per kilogram, indicating moderate tissue distribution beyond the plasma compartment. Plasma protein binding is approximately 70 percent, predominantly to albumin [3, 8]. Central nervous system penetration is inferred from the neuroprotective and anticonvulsant effects observed in preclinical models [10, 25], though direct

measurement of cerebrospinal fluid concentrations in humans has not been published. The compound's moderate molecular weight and limited polar surface area are consistent with passive blood-brain barrier permeation.

5.3 Metabolism

Macimorelin is metabolized predominantly in the liver by cytochrome P450 3A4 (CYP3A4) [3, 8]. The principal metabolic transformation is O-demethylation, producing a major circulating metabolite that retains partial GHS-R1a agonist activity but at lower potency than the parent compound [3]. Additional minor metabolic pathways include peptide bond hydrolysis and oxidative modifications of the indole rings.

The CYP3A4 dependence creates clinically relevant drug interactions. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, nefazodone) increase macimorelin plasma concentrations and may potentiate the growth hormone response [8]. Conversely, strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, enzalutamide, mitotane, St. John's wort, bosentan, efavirenz, etravirine, modafinil, armodafinil, rufinamide) decrease macimorelin exposure and may reduce the growth hormone response, potentially producing false-positive diagnostic results [8]. The prescribing label recommends discontinuing strong CYP3A4 inducers for an appropriate washout period (at least five half-lives of the inducer) before the macimorelin test.

5.4 Elimination

The terminal elimination half-life is approximately 4.1 hours (plus or minus 1.2 hours) at the 0.5 mg/kg dose in healthy adults [6, 7]. At higher doses (2.0 mg/kg), the half-life extends to approximately 8.3 hours, suggesting saturable elimination or nonlinear pharmacokinetics at supratherapeutic doses [7].

Excretion is predominantly fecal (approximately 75 percent of the absorbed dose), with minor urinary elimination (approximately 10 percent) [3, 8]. Less than 5 percent of the administered dose is excreted unchanged in urine, consistent with the predominantly hepatic metabolic elimination. The fecal route likely reflects both biliary excretion of metabolites and incomplete absorption of the parent compound.

5.5 Routes of administration

The sole approved route is oral administration as a reconstituted solution. The compound is supplied as granules (60 mg per sachet) for reconstitution in water to produce a 0.5 mg/mL oral solution. For patients weighing 120 kg or less, one sachet is reconstituted in 120 mL of water; for patients weighing more than 120 kg, two sachets are reconstituted in 240 mL [8]. No parenteral formulations are approved or commercially available, though intravenous and subcutaneous administration have been used in early pharmacokinetic studies. The oral route is pharmacologically appropriate because the rapid absorption (T_{max} 0.5 to 0.75 hours) produces peak plasma concentrations coincident with the optimal window for growth hormone measurement.

5.6 Special populations

Pediatric pharmacokinetics have been characterized in the Phase 2 dose-escalation study in children aged 2 to 17 years [14]. Plasma macimorelin concentrations increased proportionally with dose across 0.25, 0.5, and 1.0 mg/kg dose levels. Maximum plasma concentrations were observed between 30 and 45 minutes. Mean elimination half-lives were 1.22, 1.61, and 1.71 hours for the three dose levels, shorter than the adult half-life (4.1 hours), reflecting the higher hepatic metabolic capacity per kilogram in pediatric populations [14]. No macimorelin-related adverse events were reported.

Pharmacokinetics in the elderly (over 70 years) have not been formally characterized, and the diagnostic cutoff has not been separately validated in this population. Hepatic impairment may prolong macimorelin elimination given the CYP3A4-mediated metabolic pathway, but specific dose adjustment recommendations have not been issued. Renal impairment has minimal expected effect on macimorelin pharmacokinetics given the predominantly hepatic-fecal elimination.

6. Preclinical Pharmacology

6.1 Growth hormone releasing activity in animals

In the original Guerlavais et al. (2003) characterization, macimorelin (JMV-1843) administered orally to rats at doses of 1 to 10 mg/kg produced dose-dependent elevation of plasma growth hormone exceeding the response to subcutaneous hexarelin at equimolar doses [2]. In beagle dogs, oral administration produced robust growth hormone release with bioavailability sufficient to support clinical development as an oral compound [2]. The growth hormone response was abolished by pretreatment with the GHS-R1a antagonist [D-Lys3]-GHRP-6, confirming receptor-mediated activity [2]. Compared with hexarelin (examorelin) administered subcutaneously, macimorelin administered orally significantly and selectively increased growth hormone release in rats with growth hormone levels remaining high for approximately 120 minutes after oral or intraduodenal administration [16].

6.2 Epilepsy and seizure models

Clynen and colleagues (2021) characterized macimorelin in the intrahippocampal kainic acid (IHKA) mouse model of pharmacoresistant temporal lobe epilepsy [10]. Chronic oral administration significantly decreased both the number and duration of seizures during the treatment period compared to vehicle control. The effect was anticonvulsant (suppression of ongoing seizures) rather than antiepileptogenic (prevention of epilepsy development), and was not disease-modifying in the sense of altering the long-term seizure trajectory after treatment cessation [10].

Separate work in the pilocarpine rat model of status epilepticus demonstrated that macimorelin administered prior to seizure induction increased neuronal survival in the dentate gyrus, decreased apoptosis, and reduced microglial activation [25]. These neuroprotective effects were dissociable from anticonvulsant effects, as macimorelin did not prevent pilocarpine-induced status epilepticus at the doses tested [25].

6.3 Cachexia models

Preclinical studies in tumor-bearing rodent models have demonstrated that ghrelin receptor agonism with macimorelin and related compounds attenuates body weight loss, preserves lean mass, increases food intake, and reduces circulating proinflammatory cytokines [9, 22]. The effects are consistent with the known orexi-genic and anabolic actions of ghrelin receptor activation and provide the mechanis-tic rationale for clinical investigation in cancer cachexia.

6.4 Safety pharmacology

Preclinical safety pharmacology studies conducted for regulatory submission (summarized in the FDA pharmacology review) characterized macimorelin effects on central nervous system, cardiovascular, and respiratory function [3]. No signifi-cant central nervous system effects (sedation, motor impairment, seizure liability) were observed at multiples of the human diagnostic dose. Cardiovascular evalua-tion in the hERG channel assay and in telemetry-instrumented dogs identified the QT-prolongation signal that subsequently manifested clinically as the approxi-mately 11-millisecond QTc increase [3, 8]. Respiratory function was not affected at studied doses.

7. Clinical Evidence Base

7.1 Phase 2 validation study (Garcia et al. 2013)

The first formal clinical validation of the macimorelin growth hormone stimulation test was published by Garcia, Swerdloff, and colleagues in the Journal of Clinical Endocrinology and Metabolism in 2013 [4]. This multicenter, open-label study compared the diagnostic accuracy of oral macimorelin (0.5 mg/kg) with that of the GHRH-arginine test in 48 patients with known or suspected AGHD and 50 matched healthy controls.

Key findings: macimorelin demonstrated good discrimination between AGHD patients and controls, with diagnostic accuracy comparable to GHRH-arginine. The test was simple to administer, well tolerated, and reproducible on repeat testing. Growth hormone cutoffs for optimal sensitivity and specificity were established, informing the Phase 3 study design [4].

7.2 Phase 3 pivotal trial (Garcia et al. 2018)

The pivotal Phase 3 trial that supported FDA approval was a multicenter, open-label, randomized, two-way crossover study comparing the macimorelin growth hormone stimulation test with the insulin tolerance test in 157 subjects [5]. Subjects were stratified into high-likelihood AGHD (prior pituitary surgery or radiation with at least 3 additional pituitary hormone deficiencies), intermediate-likelihood AGHD (prior pituitary disease with fewer additional deficiencies), and low-likelihood AGHD.

At the primary analysis cutoff of 2.8 ng/mL peak serum growth hormone:

- Sensitivity: 87 percent (correctly identifying AGHD patients)
- Specificity: 96 percent (correctly identifying healthy controls)
- Negative agreement with ITT: 95.4 percent (95 percent CI, 87.1 to 99.0 percent)
- Positive agreement with ITT: 74.3 percent (95 percent CI, 62.8 to 83.8 percent)
- Reproducibility on repeat testing: 97 percent concordance (33 of 34 subjects) [5]

A secondary cutoff of 5.1 ng/mL provided higher sensitivity (92 percent) with specificity maintained at 96 percent, suitable for screening applications where false-negative rates must be minimized [5]. The test performance was not significantly affected by body mass index, a notable advantage over the GHRH-arginine test which requires BMI-adjusted cutoffs [5].

7.3 Sensitivity and specificity refinement (Yuen et al. 2021)

A subsequent analysis by Yuen and colleagues (2021) examined the sensitivity and specificity of the macimorelin test across different pretest probability groups and confirmed that the 2.8 ng/mL cutoff provides optimal discrimination across the range of clinical presentations [26]. The analysis also demonstrated that combining the macimorelin test with clinical predictors (number of pituitary hormone deficiencies, structural pituitary abnormalities) produces near-perfect diagnostic accuracy in high-likelihood patients.

7.4 Cancer cachexia pilot trial (Herodes et al. 2023)

The first therapeutic application of macimorelin beyond the diagnostic indication was evaluated in a pilot randomized, double-blind, placebo-controlled trial in patients with cancer cachexia [9]. Patients with advanced solid tumors and involuntary weight loss of at least 5 percent received macimorelin or placebo orally once daily for one week. Primary endpoints were safety and tolerability; secondary endpoints included body weight change and quality of life assessment.

Results: daily oral macimorelin for one week was safe and well tolerated. A numerical improvement in body weight and quality of life was observed compared to placebo, though the study was not powered for statistical significance on efficacy endpoints [9]. The safety profile was consistent with the diagnostic studies, with no serious adverse events and mild transient adverse events (dysgeusia, nausea). These findings support the feasibility of longer-term cachexia trials but do not establish clinical efficacy.

7.5 Pediatric AGHD diagnosis

The Phase 2 pediatric study (Allas et al., 2021) demonstrated safety, tolerability, and dose-proportional pharmacokinetics and pharmacodynamics of macimorelin in children aged 2 to 17 years with suspected growth hormone deficiency [14]. Twenty-

four patients received ascending single doses (0.25, 0.5, and 1.0 mg/kg) in sequential cohorts. No macimorelin-related serious adverse events were reported. Growth hormone concentrations increased following macimorelin administration in a dose-dependent manner, with mean times to maximum growth hormone concentration of 52.5 minutes (0.25 mg/kg), 37.5 minutes (0.5 mg/kg), and 37.5 minutes (1.0 mg/kg). The 1.0 mg/kg dose produced the most robust and consistent growth hormone response and was selected for Phase 3 evaluation.

The Phase 3 DETECT trial (NCT04786873) is designed to validate macimorelin for the diagnosis of childhood-onset growth hormone deficiency using comparison with established pediatric stimulation tests (arginine, clonidine) [15]. If approved, macimorelin would be the first growth hormone stimulation test for pediatric patients validated through a randomized controlled trial.

7.6 Epilepsy (preclinical only)

Clinical trials of macimorelin in epilepsy have not been conducted. The preclinical evidence from the IHKA model supports the translational potential of ghrelin receptor agonism for seizure suppression in pharmacoresistant temporal lobe epilepsy [10], but the compound's current regulatory positioning as a diagnostic agent and the requirement for chronic dosing in epilepsy create a substantial regulatory and development distance between preclinical evidence and clinical application.

8. Sourcing and Quality Verification

Pharmaceutical-grade macimorelin (Macrilen or Ghryvelin) is the highest quality source and is the only form appropriate for diagnostic use in patients. The pharmaceutical product is supplied as a single-dose pouch containing macimorelin acetate granules (equivalent to 60 mg macimorelin free base per pouch), intended for weight-based dosing at 0.5 mg/kg [8]. Pharmaceutical sourcing requires a medical order and is subject to national prescription and diagnostic procedure regulations. Commercial availability in the United States has been intermittently limited; investigators should confirm current supply status before planning macimorelin-based studies.

Research-grade macimorelin acetate is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, MedKoo Biosciences, InvivoChem, Cayman Chemical, Selleckchem, Sigma-Aldrich, TargetMol, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the acetate salt or free base. Pricing is moderate to high for a peptidomimetic compound, typically in the range of \$100 to \$500 per 50 milligrams of research-grade material at the time of monograph preparation.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (475.24 for the protonated free base $[M+H]^+$, or 535.26 for the protonated acetate salt)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structure, particularly the diagnostic indole proton signals and the alpha-aminoisobutyric acid gem-dimethyl singlet
- Chiral HPLC or polarimetric confirmation of stereochemical integrity (D-tryptophan configuration and R-configuration at the C-terminal center)
- Residual solvent analysis appropriate for the synthetic route (common solvents: dimethylformamide, acetonitrile, trifluoroacetic acid from HPLC purification)

- Water content by Karl Fischer titration for lyophilized material

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Given the peptidomimetic nature of the compound, particular attention should be given to the absence of des-formyl or des-Aib truncation products, which can arise from incomplete coupling or from hydrolytic degradation during storage.

9. Reconstitution and Handling

9.1 Pharmaceutical product reconstitution

The marketed Macrilen product (60 mg macimorelin acetate granules per pouch) is reconstituted by a healthcare professional in approximately 120 mL of water immediately prior to administration, producing a solution at a concentration of 0.5 mg/mL [8]. The contents of the sachet should be dissolved by gentle stirring for 2 to 3 minutes. The appropriate dose volume is calculated as 1 mL per kilogram of body weight. The solution is drawn up using a syringe (without needle) and transferred to a drinking glass, from which the patient drinks the entire volume within 30 seconds. The reconstituted solution must be used within 30 minutes of preparation; unused solution must be discarded. Administration must occur after a minimum 8-hour overnight fast and at least 24 hours after the last episode of strenuous physical exercise [5, 8].

9.2 Research-grade reconstitution

For in vitro research, macimorelin acetate is freely soluble in water and in dimethyl sulfoxide (DMSO). Stock solutions are typically prepared at 10 to 50 mM in DMSO for cell-based assays or at 1 to 10 mg/mL in sterile water or phosphate-buffered saline for in vivo administration. The compound is stable in aqueous solution at pH 4 to 7 for at least 24 hours at room temperature and for at least 7 days at 2 to 8 degrees Celsius [3].

For chronic in vivo studies (such as the cachexia or epilepsy research paradigms), solutions should be prepared fresh daily or stored at minus 20 degrees Celsius in single-use aliquots. Stability data from the FDA pharmacology review indicate acceptable potency retention for 30 days when stored as a dry powder at controlled room temperature and protected from moisture [3]. Aliquoting of stock solution for single-use is recommended to avoid freeze-thaw cycles; stability through at least 5 freeze-thaw cycles has been demonstrated without measurable potency loss for DMSO stock solutions.

9.3 Storage

The solid compound (pharmaceutical-grade granules) should be stored under refrigeration at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) in the original packaging until use [8]. Research-grade material should be stored at controlled room temperature (15 to 25 degrees Celsius) in a dry environment for short-term use, or at minus 20 degrees Celsius for long-term storage (greater than 6 months). The compound is not hygroscopic under normal laboratory conditions but should be stored in sealed containers with desiccant to prevent moisture-induced degradation of the peptide bonds. The peptidomimetic structure confers substantially greater chemical stability than true peptide growth hormone secretagogues (GHRP-6, hexarelin), which require more stringent cold-chain and moisture-control measures.

10. Stack Interactions and Combinations

Macimorelin is administered as a single diagnostic dose rather than as a chronic therapeutic agent, and the drug interaction considerations are therefore focused on medications present in the patient's chronic regimen at the time of diagnostic testing. Investigators conducting research with macimorelin, especially in chronic dosing paradigms for cachexia or neuroprotection, should consider the following interaction categories:

CYP3A4 inhibitors: Strong inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, nefazodone, voriconazole, posaconazole) substantially increase macimorelin exposure [8]. In the diagnostic context, this may potentiate the growth hormone response. In the therapeutic research context, this produces elevated plasma concentrations and potentially enhanced or prolonged pharmacodynamic effects.

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital, enzalutamide, mitotane, St. John's wort, bosentan, efavirenz, etravirine, modafinil, armodafinil, rufinamide) substantially decrease macimorelin exposure [8]. In the diagnostic context, this may produce false-positive results. In the therapeutic research context, this reduces effective drug concentrations. A minimum washout period of 5 half-lives of the inducer should precede macimorelin diagnostic testing.

QT-prolonging agents: The approximately 11-millisecond QTc prolongation at the diagnostic dose is additive with other QT-prolonging agents [8]. Coadministration with antiarrhythmics (sotalol, amiodarone, dofetilide), antipsychotics (haloperidol, ziprasidone), fluoroquinolones (moxifloxacin), macrolides (erythromycin), and other QT-prolonging compounds should be avoided during the diagnostic test and approached with caution and electrocardiographic monitoring in chronic dosing research.

Somatostatin analogs: Concurrent octreotide, lanreotide, or pasireotide suppresses growth hormone release through somatostatin receptor-mediated inhibition of somatotroph secretion and may produce false-positive diagnostic results.

These agents should be held for an appropriate washout period (at least 1 month for long-acting formulations) before the macimorelin test [8].

Other ghrelin receptor agonists: Concurrent administration with other GHS-R1a agonists (anamorelin, ipamorelin, GHRP-6, GHRP-2, hexarelin, ibutamoren/MK-677) produces additive or synergistic growth hormone release [22]. The combination is pharmacologically redundant for diagnostic purposes but may be relevant for mechanistic research comparing receptor activation profiles.

Growth hormone and growth hormone-releasing agents: Exogenous growth hormone therapy should be discontinued with appropriate washout (minimum 1 month) prior to diagnostic testing, as it suppresses endogenous growth hormone secretion through negative feedback at the hypothalamic-pituitary level [8]. Concurrent GHRH or tesamorelin administration may potentiate the growth hormone response.

Corticosteroids: Chronic supraphysiologic glucocorticoid exposure may blunt the growth hormone response to macimorelin through hypothalamic-pituitary axis suppression. Physiologic replacement doses (hydrocortisone 15 to 25 mg daily or equivalent) are not expected to interfere with the test [8].

Proton pump inhibitors and antacids: The effect of gastric pH modulation on macimorelin absorption has not been formally characterized. Given the oral absorption characteristics, investigators should consider the potential for altered absorption in patients on high-dose proton pump inhibitor therapy.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed across clinical trials and postmarketing surveillance at the diagnostic dose of 0.5 mg/kg are [5, 8]:

- Dysgeusia (altered taste, typically bitter or metallic): approximately 9 percent of subjects; transient, resolving within minutes to hours without intervention
- Headache: approximately 6 percent; mild, comparable to placebo rates in controlled studies
- Dizziness: approximately 4 percent; mild, transient
- Fatigue: approximately 4 percent
- Nausea: approximately 3 percent; mild
- Hunger: approximately 3 percent; consistent with the orexigenic mechanism of GHS-R1a activation
- Diarrhea: infrequent; mild
- Upper respiratory tract infection: infrequent; of uncertain causal attribution
- Feeling hot and hyperhidrosis: infrequent; mild
- Sinus bradycardia: infrequent; asymptomatic

All adverse events reported in clinical trials have been Grade 1 (mild) in severity and self-limiting, requiring no medical intervention [5, 8]. No serious adverse events attributable to macimorelin have been reported across more than 1000 administered subjects in clinical studies.

11.2 QT interval prolongation

The single clinically relevant safety signal is prolongation of the corrected QT interval. A thorough QT study reported a mean baseline- and placebo-adjusted change in QTcF of 9.6 milliseconds (upper single-sided 95 percent confidence bound of 11.4 milliseconds) at 4 hours post-dose [3, 8]. This magnitude of prolongation is above the regulatory threshold of concern (5 milliseconds mean change, 10 milliseconds upper confidence bound) and warrants clinical attention.

QT prolongation can predispose to torsade de pointes ventricular tachycardia, with the risk increasing in the presence of predisposing factors: pre-existing QT prolongation, hypokalemia, hypomagnesemia, bradycardia, congestive heart failure, and concomitant QT-prolonging medications. The prescribing label recommends electrocardiographic monitoring in patients with known risk factors and avoidance of concomitant QT-prolonging drugs during the test [8]. No cases of torsade de pointes, syncope, or other serious cardiac events attributable to macimorelin have been reported in clinical trials or postmarketing surveillance.

11.3 Comparison to alternative test safety

The safety advantage of the macimorelin test relative to the ITT is the defining clinical benefit. The ITT requires insulin-induced hypoglycemia (blood glucose below 40 mg/dL or 2.2 mmol/L) and carries the risks of severe hypoglycemia, seizures, loss of consciousness, and cardiovascular events. The ITT is contraindicated in patients with seizure disorders, coronary artery disease, cerebrovascular disease, and adrenal insufficiency. The macimorelin test eliminates these risks entirely [5, 8, 12].

Relative to the glucagon stimulation test, the macimorelin test avoids the nausea and vomiting (reported in 30 to 50 percent of patients), headache, and abdominal pain associated with intramuscular glucagon administration and the prolonged 3- to 4-hour test duration. Relative to the GHRH plus arginine test, the macimorelin test avoids the flushing and nausea of GHRH infusion, the requirement for intravenous access, and the limited availability of GHRH in some jurisdictions [12, 13].

11.4 Safety in chronic dosing

The cancer cachexia pilot trial (one week of daily dosing) did not identify additional safety signals beyond those observed with single-dose diagnostic use [9]. However, the chronic safety profile at the diagnostic dose or higher has not been characterized in large trials. Investigators planning chronic dosing studies (for cachexia, epilepsy, or other therapeutic applications) should consider the QTc effect and the potential for cumulative growth hormone axis effects (IGF-1 elevation, fluid retention, insulin resistance) that characterize chronic ghrelin receptor agonism [22].

11.5 Pregnancy, lactation, and special populations

No human pregnancy data are available. Animal reproductive toxicology studies (FDA pharmacology review) did not demonstrate teratogenicity at multiples of the human diagnostic dose [3]. Use in pregnancy is not recommended unless the diagnostic benefit clearly outweighs the unknown risk. Lactation data are not available; the short half-life (4.1 hours) suggests that maternal exposure following a single diagnostic dose would be substantially cleared within 24 hours.

Pediatric safety has been characterized in the Phase 2 dose-escalation study, with no safety signals identified [14]. Geriatric patients have been included in the diagnostic trials without specific safety concerns [5].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five growth hormone secretagogue or AGHD diagnostic candidates against macimorelin, evaluated against five competency standards: novelty, effect size (diagnostic accuracy or therapeutic effect), promising potential (current clinical state and trajectory), side-effect profile, and overall validation.

12.1 Insulin Tolerance Test (ITT)

Mechanism: Induction of hypoglycemia through intravenous insulin (0.1 to 0.15 IU/kg) to activate the counter-regulatory stress response, which includes growth hormone release through hypothalamic GHRH secretion and direct pituitary activation [12].

Novelty: None. The ITT was established in the 1960s and remains the reference standard for AGHD diagnosis by consensus guidelines.

Effect size (diagnostic accuracy): Sensitivity and specificity are reference-standard by definition but are estimated at 85 to 100 percent depending on the population, the growth hormone cutoff employed (typically 3.0 to 5.0 ng/mL), and the growth hormone assay used [12]. The ITT also tests the hypothalamic-pituitary-adrenal axis simultaneously (cortisol response), providing additional diagnostic information.

Promising potential: Stable. The ITT will remain the reference standard in guidelines but is increasingly supplemented or replaced by safer alternatives in clinical practice.

Side-effect profile: The principal limitation is the requirement for symptomatic hypoglycemia (blood glucose less than 2.2 mmol/L, or 40 mg/dL). Adverse events include diaphoresis, tachycardia, tremor, seizures (rare), and loss of consciousness. The test is contraindicated in patients with seizure disorders, coronary artery disease, cerebrovascular disease, and the elderly. Medical supervision with intravenous access and available dextrose is mandatory throughout the procedure [12].

Overall validation: Maximum. The ITT is the most extensively validated test for AGHD with decades of clinical experience and consensus guideline endorsement. Its limitations are practical (safety, contraindications, provider burden) rather than diagnostic.

Comparison to macimorelin: Macimorelin provides comparable diagnostic accuracy (87 percent sensitivity and 96 percent specificity versus the ITT reference) without the requirement for hypoglycemia induction, intravenous access, or extended monitoring [5]. The ITT provides additional hypothalamic-pituitary-adrenal axis information that macimorelin does not. For routine clinical diagnosis of isolated AGHD, macimorelin represents a safer, simpler alternative with minimal accuracy trade-off.

12.2 Glucagon Stimulation Test (GST)

Mechanism: Intramuscular glucagon (1 mg) stimulates growth hormone release through an incompletely characterized mechanism, possibly involving stimulation of GHRH secretion or modulation of hypothalamic somatostatin tone [12].

Novelty: Low. The GST has been in clinical use since the 1970s as an alternative to the ITT.

Effect size (diagnostic accuracy): Sensitivity 73 to 100 percent, specificity 71 to 100 percent depending on the growth hormone cutoff (typically 3.0 ng/mL) and the population studied [12]. Performance is generally considered acceptable but less well validated than the ITT. A lower growth hormone cutpoint of 1 ng/mL has been proposed for overweight and obese patients. BMI-adjusted cutoffs are recommended, adding complexity to interpretation [27].

Promising potential: Declining. The availability of macimorelin as a simpler oral alternative has reduced enthusiasm for the GST, though it remains available and guideline-endorsed in jurisdictions where macimorelin is unavailable.

Side-effect profile: Nausea and vomiting (30 to 50 percent), headache, abdominal pain. The test requires intramuscular injection and 3 to 4 hours of monitoring. It is contraindicated in patients with pheochromocytoma or insulinoma and should be used with caution in malnourished patients [12].

Overall validation: Moderate. The GST has substantial clinical experience but less formal validation than the ITT. The growth hormone cutoff is less precisely established and requires BMI adjustment.

Comparison to macimorelin: Macimorelin is simpler to administer (oral versus intramuscular), requires shorter monitoring (90 minutes versus 3 to 4 hours), produces fewer adverse events (mild dysgeusia versus substantial nausea/vomiting), uses a single universal cutoff (2.8 ng/mL) regardless of BMI, has better reproducibility (97 percent versus approximately 90 percent for GST), and has formal Phase 3 validation [5]. The GST remains useful as an alternative where macimorelin is unavailable or in patients with potential CYP3A4 interactions.

12.3 Anamorelin (ONO-7643, RC-1291)

Mechanism: Non-peptide, orally active GHS-R1a agonist structurally unrelated to macimorelin. Full agonist at the ghrelin receptor with binding affinity K_i approximately 0.7 nanomolar [28].

Novelty: Moderate. Anamorelin represents the only approved therapeutic ghrelin receptor agonist (approved in Japan in 2021 for cancer cachexia).

Effect size: In the ROMANA-1 and ROMANA-2 Phase 3 trials (total enrollment approximately 950 patients with non-small cell lung cancer cachexia), anamorelin at 100 mg daily for 12 weeks significantly increased lean body mass (median increase 0.6 to 1.0 kg versus placebo) and body weight but did not significantly improve handgrip strength (the co-primary endpoint), leading to regulatory rejection in some jurisdictions [28, 29]. Growth hormone and IGF-1 levels were substantially elevated.

Promising potential: Moderate. Approved in Japan for cancer cachexia. Not approved by the FDA or EMA for any indication (the FDA declined the cachexia NDA based on the handgrip strength endpoint failure). Available as a research compound.

Side-effect profile: Generally well tolerated. Principal adverse events include hyperglycemia (related to growth hormone axis activation), nausea, and peripheral edema. QTc prolongation has been characterized at therapeutic doses [28].

Overall validation: Moderate to high for the cachexia mechanism; high receptor-level validation as a GHS-R1a agonist. Cryo-EM structural studies have characterized the binding mode of anamorelin at the GHS-R1a receptor at high resolution, providing molecular comparison with macimorelin [24]. The negative handgrip strength endpoint in Phase 3 limits overall clinical validation despite lean mass improvements.

Comparison to macimorelin: Anamorelin and macimorelin share the GHS-R1a target but occupy entirely different clinical positions. Macimorelin is a diagnostic agent with single-dose use and regulatory approval in the United States and Europe; anamorelin is a therapeutic agent with chronic dosing and approval only in Japan. For research into ghrelin receptor pharmacology, anamorelin provides the chronic-dosing therapeutic reference while macimorelin provides the acute-dosing diagnostic reference. Macimorelin has more robust clinical validation for its indicated use (diagnostic) than anamorelin has for its therapeutic use (cachexia endpoint partially negative).

12.4 Ibutamoren (MK-677)

Mechanism: Non-peptide, orally active GHS-R1a agonist derived from a spiroindanylpiperidine scaffold [30]. Full agonist at the GHS-R1a receptor with sustained growth hormone release over 24 hours on once-daily oral dosing, reflecting its long elimination half-life (approximately 24 hours).

Novelty: Moderate. Ibutamoren was among the earliest orally active growth hormone secretagogues characterized in the 1990s and has been extensively studied in healthy volunteers and elderly populations.

Effect size: In clinical trials, ibutamoren at 25 mg daily for 12 months significantly increased growth hormone pulsatility, IGF-1 concentrations (40 to 60 percent increase), lean body mass, and basal metabolic rate in healthy elderly subjects [30, 31]. However, the compound failed to demonstrate clinically meaningful improvements in functional endpoints (strength, physical performance) in the hip fracture recovery population and other studied populations [31].

Promising potential: Low for regulatory approval. Ibutamoren is not approved by any regulatory agency for any indication. It was abandoned by Merck after Phase 2 studies failed to demonstrate functional benefit despite biochemical improvement. The compound is widely available as a research chemical [30].

Side-effect profile: Common adverse events include appetite stimulation and weight gain (reflecting hypothalamic GHS-R1a activation), mild edema and fluid retention, transient mild hyperglycemia, and rare arthralgia. The 24-hour duration of action produces more sustained appetite stimulation than the shorter-acting secretagogues [30, 31].

Overall validation: Moderate for the growth hormone secretagogue mechanism; low for clinical utility in any therapeutic indication. Extensive Phase 2 human data but no approved indication.

Comparison to macimorelin: Ibutamoren and macimorelin target the same receptor but occupy fundamentally different clinical niches. Macimorelin is a diagnostic agent (single dose, short half-life, transient growth hormone release) with FDA and EMA approval; ibutamoren is an unapproved therapeutic candidate (chronic dosing, long half-life, sustained growth hormone and IGF-1 elevation). Macimorelin has the advantage of regulatory approval and validated diagnostic application; ibutamoren has the advantage of extensive chronic-dosing pharmacology data. The two compounds are complementary research tools for understanding acute versus chronic GHS-R1a pharmacology.

12.5 GHRH-Arginine Test

Mechanism: Combined administration of growth hormone releasing hormone (GHRH, 1 microgram/kg intravenous) and arginine (0.5 g/kg intravenous over 30 minutes) produces synergistic growth hormone release through complementary hypothalamic and pituitary stimulation [13].

Novelty: None. The GHRH-arginine combination was established in the 1990s as an alternative to the ITT for AGHD diagnosis.

Effect size (diagnostic accuracy): Sensitivity 95 to 100 percent, specificity 91 to 97 percent at BMI-adjusted cutoffs (cutoffs range from 4.1 to 11.5 ng/mL depending on BMI) [13]. The GHRH-arginine test has among the highest diagnostic accuracies of any GHD stimulation test when BMI-appropriate cutoffs are applied.

Promising potential: Declining in the United States; stable elsewhere. Synthetic GHRH (Geref Diagnostic) was withdrawn from the United States market in 2008 due to a manufacturing decision unrelated to safety or efficacy, leaving the test unavailable in the United States [13]. In Europe, Japan, and other jurisdictions where GHRH remains available, the test continues to be used and is guideline-endorsed.

Side-effect profile: Mild facial flushing from GHRH (transient), nausea from arginine infusion (mild to moderate). Requires intravenous access and 90 to 120 minutes of monitoring. No hypoglycemia induction. Generally well tolerated [13].

Overall validation: High in jurisdictions where available. The test has extensive validation data and guideline endorsement. The principal limitation in the United States is unavailability of GHRH rather than any performance concern.

Comparison to macimorelin: Macimorelin was initially validated against GHRH-arginine in the Phase 2 study (Garcia et al. 2013) and demonstrated comparable accuracy [4]. The principal advantage of macimorelin is oral administration without intravenous access, shorter procedure time, a single universal cutoff regardless of BMI (versus the BMI-adjusted cutoffs required for GHRH-arginine), and availability in the United States where GHRH is not marketed. The GHRH-arginine test may have marginally higher sensitivity in some populations but requires intravenous access and is unavailable in the United States.

12.6 Comparator summary

The five comparators occupy distinct positions in the GHD diagnostic and growth hormone secretagogue landscape. The **ITT** remains the gold standard diagnostic but is limited by safety concerns and contraindications that restrict its use in a substantial fraction of the AGHD patient population. The **GST** is a widely available but less precise alternative with substantial adverse events and a prolonged test duration. **Anamorelin** represents the therapeutic GHS-R1a agonist class with chronic cachexia dosing rather than diagnostic application, approved only in Japan. **Ibutamoren** is the historically important oral GHS-R1a agonist that failed to achieve regulatory approval despite biochemical efficacy and extensive Phase 2 data. The **GHRH-arginine test** offers high diagnostic accuracy but is unavailable in the United States and requires BMI-adjusted cutoffs.

Macimorelin occupies a unique position as the only oral, single-dose, FDA- and EMA-approved diagnostic for AGHD, combining the convenience of oral administration with the pharmacological specificity of GHS-R1a agonism and formal Phase 3 validation against the ITT gold standard. Its safety profile (no serious adverse events across more than 1000 subjects) is superior to the ITT and GST for the diagnostic application, and its regulatory validation exceeds that of any other oral growth hormone secretagogue for any approved indication. Its single universal cutoff of 2.8 ng/mL (without BMI adjustment) simplifies clinical application relative to

the GHRH-arginine test. The principal limitation is the diagnostic (rather than therapeutic) positioning, which restricts the immediate clinical utility to a single-use test, though the cachexia, neuroprotection, and pediatric research programs may expand the clinical applications.

For investigators, macimorelin provides a well-characterized, pharmacologically specific GHS-R1a agonist tool with established human pharmacokinetic and safety data, suitable for diagnostic research, acute growth hormone axis challenge studies, and as a comparator or mechanistic probe in ghrelin receptor biology research.

13. References

1. Fehrentz JA, Martinez J, Guerlavais V, et al. Novel orally active growth hormone secretagogues. International patent WO 00/01726. CNRS/University of Montpellier. Filed 1999.
2. Guerlavais V, Boeglin D, Mousseaux D, et al. New active series of growth hormone secretagogues. *J Med Chem*. 2003;46(7):1191-1203.
3. Center for Drug Evaluation and Research. Application Number 205598Orig1s000. Pharmacology Review. U.S. Food and Drug Administration. 2017.
4. Garcia JM, Swerdloff R, Wang C, et al. Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab*. 2013;98(6):2422-2429.
5. Garcia JM, Biller BMK, Korbonits M, et al. Macimorelin as a diagnostic test for adult GH deficiency. *J Clin Endocrinol Metab*. 2018;103(8):3083-3093.
6. Piccoli F, Degen L, MacLean C, et al. Pharmacokinetics and pharmacodynamic effects of an oral ghrelin agonist in healthy subjects. *J Clin Endocrinol Metab*. 2007;92(5):1814-1820.
7. Piccoli F, Degen L, MacLean C, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of macimorelin in healthy adults: results of a single-dose, randomized controlled study. *Growth Horm IGF Res*. 2020;52:101321.
8. Macrilen (macimorelin) prescribing information. Aeterna Zentaris. U.S. Food and Drug Administration approved label. December 2017. NDA 205598.
9. Herodes M, Gonuguntla K, Engel J, et al. Pilot clinical trial of macimorelin to assess safety and efficacy in patients with cancer cachexia. *J Cachexia Sarcopenia Muscle*. 2023;14(2):920-928.
10. Clynen E, Swijsen A, Raber J, et al. Translational potential of the ghrelin receptor agonist macimorelin for seizure suppression in pharmacoresistant epilepsy. *Neurotherapeutics*. 2021;18(3):1896-1908.

11. Zhao W, Guerrero A, Zhou D, et al. Advances in the development of nonpeptide small molecules targeting ghrelin receptor. *J Med Chem.* 2022;65(6):4191-4218.
12. Yuen KCJ, Tritos NA, Samson SL, et al. Growth hormone stimulation tests in assessing adult growth hormone deficiency. In: Feingold KR, et al., eds. *Endotext.* South Dartmouth, MA: MDText.com; 2000 (updated 2022).
13. Aimaretti G, Corneli G, Razzore P, et al. Comparison between insulin-induced hypoglycemia and growth hormone (GH)-releasing hormone plus arginine as provocative tests for the diagnosis of GH deficiency in adults. *J Clin Endocrinol Metab.* 1998;83(5):1615-1618.
14. Allas S, Puri V, Engel S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of macimorelin in children with suspected growth hormone deficiency: an open-label, group comparison, dose-escalation trial. *Horm Res Paediatr.* 2021;94(7-8):239-248.
15. ClinicalTrials.gov. Macimorelin and arginine and clonidine in growth hormone deficiency (DETECT). NCT04786873.
16. Broglio F, Boutignon F, Benso A, et al. EP1572: a novel peptido-mimetic GH secretagogue with potent and selective GH-releasing activity in man. *J Endocrinol Invest.* 2002;25(10):RC26-RC28.
17. U.S. Food and Drug Administration. FDA approves Macrilen (macimorelin) for diagnosis of adult growth hormone deficiency. December 20, 2017.
18. European Medicines Agency. Ghryvelin (macimorelin): EPAR public assessment report. 2019.
19. Aeterna Zentaris. Aeterna Zentaris amends license agreement with Novo Nordisk for commercialization and development of macimorelin. Press release, November 16, 2020.
20. Pharmanovia. Pharmanovia to market GHRYVELIN (macimorelin) in the European Economic Area (EEA) and UK as diagnostic test for growth hormone deficiency (GHD). Press release, March 16, 2023.
21. 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.

22. Muller TD, Nogueiras R, Andermann ML, et al. Ghrelin. *Mol Metab.* 2015;4(6):437-460.
 23. Holst B, Cygankiewicz A, Jensen TH, Ankersen M, Schwartz TW. High constitutive signaling of the ghrelin receptor: identification of a potent inverse agonist. *Mol Endocrinol.* 2003;17(11):2201-2210.
 24. Li M, Sun Y, Sun B, et al. Molecular recognition of two approved drugs macimorelin and anamorelin by the growth hormone secretagogue receptor. *Acta Pharmacol Sin.* 2025. doi:10.1038/s41401-025-01606-7.
 25. Lucchi C, Costa AM, Gualtieri F, et al. Protective but not anticonvulsant effects of ghrelin and JMV-1843 in the pilocarpine model of status epilepticus. *PLoS One.* 2013;8(8):e72716.
 26. Yuen KCJ, Biller BMK, Engel SS, et al. Sensitivity and specificity of the macimorelin test for diagnosis of AGHD. *Endocr Connect.* 2021;10(1):76-83.
 27. Hamrahian AH, Yuen KCJ, Gordon MB, et al. Revised GH and cortisol cut-points for the glucagon stimulation test in the evaluation of GH and cortisol deficiency in adults: results from a prospective observational study. *Pituitary.* 2016;19(3):332-341.
 28. Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol.* 2016;17(4):519-531.
 29. Currow DC, Temel JS, Abernethy AP, et al. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. *Ann Oncol.* 2017;28(8):1949-1956.
 30. Murphy MG, Plunkett LM, Gertz BJ, et al. MK-677, an orally active growth hormone secretagogue, reverses diet-induced catabolism. *J Clin Endocrinol Metab.* 1998;83(2):320-325.
 31. Nass R, Pezzoli SS, Oliveri MC, et al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. *Ann Intern Med.* 2008;149(9):601-611.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes outside the approved indication. Not for human consumption outside of properly supervised diagnostic testing. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Macimorelin is approved by the United States Food and Drug Administration and the European Medicines Agency for the diagnosis of adult growth hormone deficiency. The compound is not approved for therapeutic (cachexia, neuroprotection, epilepsy) indications. Investigators should consult their local regulatory authority before any human research application beyond the approved diagnostic indication.