

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tabimorelin

A modified polypeptide derived from ipamorelin at Novo Nordisk, representing the first orally bioavailable peptidomimetic ghrelin receptor agonist advanced to Phase 2 clinical evaluation for adult growth hormone deficiency, distinguished by mechanism-based CYP3A4 inhibition and GH-axis tachyphylaxis that limited its clinical development.

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ABSTRACT

Tabimorelin (NN703; CAS 193079-69-5; molecular formula $C_{32}H_{40}N_4O_3$; molecular weight 528.70) is a potent, orally active agonist of the growth hormone secretagogue receptor type 1a (GHSR1a, the ghrelin receptor), developed by Novo Nordisk as a non-injectable alternative to recombinant growth hormone therapy in adult growth hormone deficiency. The compound was derived from the selective pentapeptide growth hormone secretagogue ipamorelin (NNC 26-0161) through systematic backbone reduction and pharmacophore optimization conducted principally by Ankersen, Hansen, and colleagues in the late 1990s, yielding a tripeptide-like structure with oral bioavailability of approximately 30 percent in dogs and a plasma half-life of approximately 4.1 hours in the same species [1]. Tabimorelin binds the GHSR1a receptor and activates the Gq/11-coupled phospholipase C signaling cascade, producing calcium mobilization from intracellular stores, membrane depolarization, and pulsatile growth hormone release from anterior pituitary somatotroph cells. In single-dose Phase 1 studies in healthy male volunteers at doses of 0.05 to 12 mg/kg, the compound produced dose-dependent increases in growth hormone area under the curve and peak concentration, with significant elevations in GH AUC at 3.0 mg/kg ($P = 0.027$), 6.0 mg/kg ($P = 0.0023$), and 12 mg/kg ($P < 0.0001$), together with significant increases in insulin-like growth factor 1 (IGF-1) at the two highest dose levels [2]. In a 7-day repeated-dose Phase 1 study at four dose levels (1.71, 3.0, 4.5, and 6.86 mg/kg once daily), GH release remained significantly elevated above placebo on both days 1 and 7, but an overall significant decrease in GH release from day 1 to day 7 ($P < 0.001$)

demonstrated tachyphylaxis at the somatotroph axis level [3]. IGF-1 and IGF binding protein 3 (IGFBP-3) increased at all dose levels, with significantly greater IGF-1 elevation at the three highest doses. The compound produced transient increases in prolactin and adrenocorticotrophic hormone (ACTH) on day 1 that resolved by day 7, with no significant cortisol elevation on either assessment day [3]. The pivotal Phase 2 study enrolled 97 adults with confirmed growth hormone deficiency in a multicentre, randomized, double-blind, placebo-controlled design; only 9 of 83 NN703-treated patients (11 percent) achieved a serum peak GH concentration of 5 micrograms per liter or greater, and 1-week treatment did not significantly increase IGF-1, although IGFBP-3 was modestly elevated [4]. The limited clinical response was attributed to the severity of hypothalamic-pituitary axis disruption in the GH-deficient population, which depends on residual somatotroph capacity for a secretagogue mechanism to function. A separate clinical pharmacology investigation established that tabimorelin is a mechanism-based (irreversible) inhibitor of cytochrome P450 3A4, increasing midazolam AUC by 64 percent after a single dose and by 93 percent after 7 days of dosing, with persistent 45 percent elevation even after a 7-day washout [5]. This CYP3A4 liability, combined with the modest clinical efficacy in the target population and the GH tachyphylaxis on repeated dosing, led Novo Nordisk to discontinue clinical development. Tabimorelin remains a research-grade compound of interest for fundamental GHSR1a pharmacology, for structure-activity investigation within the peptidomimetic ghrelin agonist class, and as a comparator in the broader landscape of growth hormone secretagogues that includes ibutamoren (MK-0677), anamorelin, macimorelin, and capromorelin. The compound is not approved by any regulatory authority for human therapeutic

use. It is supplied as a research-grade preparation by multiple chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Tabimorelin. The name was assigned during Novo Nordisk clinical development but was not advanced to regulatory registration in any jurisdiction.

Development code: NN703 (Novo Nordisk). The NN703 designation is the canonical identifier in the primary pharmacology and clinical pharmacology literature and is the only identifier under which the Phase 1 and Phase 2 clinical data were published [1, 2, 3, 4, 5].

Chemical Abstracts Service registry number: 193079-69-5 (free base). The hemifumarate salt (CAS not separately assigned in the primary literature) is the formulated salt used in some clinical preparations and is commercially available as a research-grade material.

International Union of Pure and Applied Chemistry name: N-[(2E)-5-amino-5-methylhex-2-enoyl]-N-methyl-3-(naphthalen-2-yl)-D-alanyl-N,N-alpha-dimethyl-D-phenylalaninamide. The name reflects the linear tripeptide-like backbone with the N-terminal unsaturated amino acid residue, the central N-methyl-D-2-naphthylalanine, and the C-terminal N,N-alpha-dimethyl-D-phenylalanine amide.

Other synonyms: NN-703, tabimorelin hemifumarate (salt form).

1.2 Structural class and chemistry

Tabimorelin is a peptidomimetic growth hormone secretagogue belonging to the class of synthetic ghrelin receptor (GHSR1a) agonists. The compound represents a backbone-reduced derivative of the pentapeptide ipamorelin (Aib-His-D-2-Nal-D-Phe-Lys-NH₂), in which the five-residue peptide chain was truncated to a tripeptide-like scaffold and the backbone amide bonds were modified to reduce hydrogen-bonding potential and enhance oral bioavailability [6, 7]. The structural class places tabimorelin within the peptidomimetic subgroup of growth hormone secret-

agogues, distinct from the non-peptide small-molecule class (represented by ibutamoren/MK-0677 and macimorelin) and from the peptide class (represented by GHRP-6, GHRP-2, hexarelin, and ipamorelin itself).

Molecular formula: C₃₂H₄₀N₄O₃ (free base).

Molecular weight: 528.70 g/mol (free base).

Exact mass: 528.3101 g/mol (free base, monoisotopic).

Physical properties: White to off-white powder or lyophilized solid. Soluble in dimethyl sulfoxide (DMSO) at concentrations exceeding 50 mM; sparingly soluble in aqueous buffers at neutral pH. The hemifumarate salt improves aqueous solubility for formulation purposes. Storage at minus 20 degrees Celsius in desiccated conditions is recommended for long-term stability of the solid material.

Stereochemistry: The compound contains two stereocenters, both in the D-configuration: the central 2-naphthylalanine residue and the C-terminal phenylalanine residue are both D-amino acid derivatives. The E-configuration of the double bond in the N-terminal unsaturated chain is specified in the IUPAC name. Investigators acquiring research-grade tabimorelin should confirm stereochemical integrity by chiral chromatography or by nuclear magnetic resonance spectroscopy against published spectral data.

1.3 Synthesis

The synthesis of tabimorelin was developed at Novo Nordisk by Ankersen, Peschke, and colleagues as part of a systematic medicinal chemistry program to derive orally bioavailable growth hormone secretagogues from the pentapeptide lead ipamorelin [6, 7, 8]. The published synthetic approach proceeds through the following principal stages: preparation of the N-terminal (2E)-5-amino-5-methylhex-2-enoyl fragment by standard unsaturated amino acid synthesis; preparation of the central N-methyl-D-2-naphthylalanine building block by N-methylation of the protected D-2-naphthylalanine; preparation of the C-terminal N,N-dimethyl-D-phenylalanine amide; and sequential peptide-bond-forming reactions using standard carbodiimide or active ester coupling chemistry to assemble the tripeptide backbone [6].

The medicinal chemistry rationale was to reduce the molecular size and hydrogen-bonding donor count of ipamorelin (five backbone NH donors, five backbone CO acceptors, multiple side-chain polar groups) to below the threshold associated with oral absorption. The reduction from a pentapeptide to a modified tripeptide was accomplished by removing the N-terminal aminoisobutyric acid and histidine residues and replacing them with a single lipophilic unsaturated chain, and by N-methylating the central amide bond to remove one hydrogen-bond donor [7]. This approach yielded oral bioavailability of approximately 30 percent in dogs (compared to effectively zero for the parent pentapeptide ipamorelin) while retaining nanomolar-range potency at the GHSR1a receptor [1].

Subsequent medicinal chemistry optimization produced hybrid compounds incorporating pharmacophores from both NN703 and ipamorelin, some of which demonstrated in vitro EC50 values in the low nanomolar range and oral bioavailabilities exceeding 40 percent, although none of these successors advanced to clinical development [8, 9].

2. Abstract

Tabimorelin (NN703) is a potent, orally active peptidomimetic agonist of the growth hormone secretagogue receptor type 1a (GHSR1a), developed by Novo Nordisk in the late 1990s as an oral alternative to daily recombinant growth hormone injections for the treatment of adult growth hormone deficiency [1, 2]. The compound was derived from the pentapeptide ipamorelin through systematic backbone reduction and pharmacophore optimization, yielding a tripeptide-like structure with oral bioavailability of approximately 30 percent, a plasma half-life of approximately 4.1 hours in dogs, and retained nanomolar-range potency at the ghrelin receptor [1].

The compound entered clinical evaluation at Novo Nordisk through a series of Phase 1 studies in healthy male volunteers and a pivotal Phase 2 study in adults with confirmed growth hormone deficiency. In single-dose Phase 1 studies, tabimorelin produced dose-dependent, statistically significant increases in serum growth hormone at doses of 1.5 mg/kg and above, with corresponding elevations in IGF-1 at the highest dose levels [2]. In a 7-day repeated-dose Phase 1 study, GH release was significantly elevated above placebo at all active dose levels on both the first and seventh treatment days, but a significant overall decline in GH secretory response from day 1 to day 7 indicated somatotroph-level tachyphylaxis [3]. This tachyphylaxis, while not unexpected for ghrelin receptor agonists, reduced the magnitude of sustained GH elevation achievable with chronic oral dosing.

The Phase 2 study in 97 growth hormone-deficient adults demonstrated that only 11 percent of NN703-treated patients achieved a clinically meaningful GH peak (5 micrograms per liter or greater), that 1-week treatment did not increase IGF-1, and that benefit was confined to patients with the most moderately severe deficiency who retained residual pituitary somatotroph function [4]. This result reflected the fundamental pharmacological limitation of a secretagogue strategy in severe GH deficiency: the mechanism requires intact somatotroph cells capable of synthesizing and releasing GH in response to receptor activation, and patients with complete hypothalamic-pituitary structural damage lack this substrate.

A concurrent clinical pharmacology investigation revealed that tabimorelin is a mechanism-based (irreversible) inhibitor of CYP3A4, the principal hepatic cytochrome P450 isoform responsible for the metabolism of approximately 50 percent

of marketed drugs [5]. The CYP3A4 inhibition increased midazolam exposure by 64 percent after a single NN703 dose and by 93 percent after repeated dosing, with persistent elevation of 45 percent after a 7-day washout period. The clinical significance of this finding was considerable: chronic oral dosing of tabimorelin would substantially increase the exposure and the toxicity risk of CYP3A4 substrates administered concurrently, including immunosuppressants, statins, calcium channel blockers, protease inhibitors, and benzodiazepines.

The combination of modest clinical efficacy in the target population, GH tachyphylaxis on repeated dosing, and clinically significant CYP3A4 inhibition led Novo Nordisk to discontinue clinical development of tabimorelin. The compound was not advanced to Phase 3, was not submitted for regulatory approval in any jurisdiction, and is not marketed for human use. It remains available as a research-grade compound from multiple chemical suppliers and serves as a reference ligand for GHSR1a pharmacology, as a comparator in the peptidomimetic growth hormone secretagogue class, and as a historical case study in the challenges of translating ghrelin-mimetic pharmacology to clinically effective growth hormone replacement therapy.

3. Discovery and Development History

3.1 Origin

The discovery of tabimorelin originated in the Novo Nordisk growth hormone secretagogue program in Copenhagen, Denmark, in the mid-to-late 1990s. The program was motivated by the clinical limitation of recombinant growth hormone therapy, which requires daily subcutaneous injection and produces supraphysiological GH peaks rather than the pulsatile secretory pattern of endogenous growth hormone. An orally active compound that stimulated endogenous GH secretion in a pulsatile pattern would potentially offer advantages in patient compliance, physiological hormone replacement, and cost.

3.2 Derivation from ipamorelin

The immediate precursor compound was ipamorelin (NNC 26-0161), a pentapeptide growth hormone secretagogue identified at Novo Nordisk in the late 1990s from a structure-activity series derived from growth hormone-releasing peptide 1 (GHRP-1) [10]. Ipamorelin was characterized as the first selective growth hormone secretagogue: unlike GHRP-6 and GHRP-2, ipamorelin stimulated GH release without producing concomitant increases in ACTH, cortisol, or prolactin, and was interpreted as demonstrating that GH selectivity could be achieved within the GHSR1a agonist class [10]. However, ipamorelin, as a pentapeptide, had effectively zero oral bioavailability and required parenteral administration, limiting its clinical utility as a chronic therapy.

The Ankersen, Hansen, Peschke, and Lau medicinal chemistry team at Novo Nordisk undertook a systematic optimization of ipamorelin for oral bioavailability [6, 7]. The strategy was to reduce molecular weight below approximately 500 daltons, to reduce the number of hydrogen-bond donors below 5 (consistent with Lipinski guidelines for oral absorption), and to retain the critical pharmacophores for GHSR1a binding. The optimization produced NN703 (tabimorelin), a tripeptide-like structure that retained the D-2-naphthylalanine and D-phenylalanine pharmacophores of ipamorelin but replaced the N-terminal Aib-His dipeptide with a single lipophilic unsaturated chain and N-methylated one backbone amide bond [6].

3.3 Preclinical characterization

Hansen et al. (1999) published the pharmacological characterization of NN703 in the European Journal of Endocrinology [1]. The compound stimulated GH release from rat pituitary cells in vitro with potency and efficacy similar to GHRP-6. In swine, intravenous NN703 produced dose-dependent GH release with a potency of 155 plus or minus 23 nmol/kg and an efficacy of 91 plus or minus 7 ng GH per milliliter of plasma. In beagle dogs, oral NN703 at 20 micromol/kg produced a 35-fold increase in peak GH concentration (49.5 plus or minus 17.8 ng/mL), with an oral bioavailability of approximately 30 percent and a plasma half-life of 4.1 plus or minus 0.4 hours [1]. Long-term oral dosing in rats (100 micromol/kg daily for 14 days) produced significantly increased body weight gain compared to vehicle, consistent with sustained GH-IGF-1 axis activation.

The cortisol signal in swine (50 percent elevation above baseline at all tested doses, non-dose-dependent) was noted as a potential concern, although the investigators interpreted the non-dose-dependent pattern as suggesting a mechanism partially distinct from the GH response [1].

3.4 Clinical development

Novo Nordisk advanced tabimorelin through three principal clinical studies between approximately 1999 and 2002:

The first-in-human Phase 1 single-dose ascending study (Zdravkovic et al. 2000) enrolled healthy male volunteers at eight dose levels (0.05 to 12 mg/kg), establishing dose-dependent GH release, safety, and tolerability [2].

The Phase 1 repeated-dose study (Zdravkovic et al. 2000) evaluated 7 days of once-daily oral dosing at four dose levels (1.71, 3.0, 4.5, and 6.86 mg/kg), demonstrating sustained but attenuated GH release (tachyphylaxis), IGF-1 elevation, and transient non-GH hormonal effects [3].

The Phase 2 study in adult GH deficiency (Svensson et al. 2003) was the pivotal efficacy evaluation, demonstrating that only a small minority of GH-deficient adults responded to the secretagogue mechanism and that IGF-1 was not meaningfully elevated by 1-week treatment [4].

3.5 Discontinuation

The clinical development of tabimorelin was discontinued by Novo Nordisk following the Phase 2 results and the CYP3A4 interaction finding. The decision reflected three converging factors: the limited GH response rate in the target population (11 percent), the GH tachyphylaxis on repeated dosing, and the mechanism-based CYP3A4 inhibition that would produce clinically significant drug-drug interactions with chronic use [5]. Novo Nordisk subsequently explored successor compounds derived from NN703, including NNC-26-1167 and hybrid structures incorporating pharmacophores from both NN703 and ipamorelin, but none of these advanced to clinical evaluation [8, 9].

4. Mechanism of Action

Tabimorelin is a synthetic agonist of the growth hormone secretagogue receptor type 1a (GHSR1a), the G protein-coupled receptor that serves as the endogenous receptor for the 28-amino-acid acylated peptide hormone ghrelin. The compound mimics the pharmacological action of ghrelin at the pituitary somatotroph, producing growth hormone release through a signaling cascade that is mechanistically distinct from, and synergistic with, growth hormone-releasing hormone (GHRH) stimulation.

4.1 GHSR1a receptor pharmacology

The GHSR1a receptor was identified by Howard et al. (1996) through expression cloning of a cDNA encoding a G protein-coupled receptor activated by the synthetic hexapeptide growth hormone-releasing peptide MK-0677 [11]. The endogenous ligand ghrelin was subsequently identified by Kojima et al. (1999) as a 28-amino-acid peptide produced predominantly by X/A-like enteroendocrine cells of the gastric oxyntic mucosa, with an essential octanoyl modification on serine-3 catalyzed by the enzyme ghrelin O-acyltransferase (GOAT) [12].

GHSR1a is a seven-transmembrane G protein-coupled receptor of the class A (rhodopsin-like) family. It is expressed at high density on anterior pituitary somatotroph cells, in the hypothalamic arcuate nucleus (on neuropeptide Y/agouti-related peptide neurons), in the ventromedial hypothalamus, in the nucleus tractus solitarius, in the area postrema, and at lower density in the hippocampus, ventral tegmental area, and substantia nigra. The receptor signals primarily through the heterotrimeric Gq/11 protein, activating phospholipase C-beta (PLC-beta), which catalyzes hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 triggers calcium release from endoplasmic reticulum stores; DAG activates protein kinase C (PKC), which inhibits potassium channels and produces membrane depolarization; depolarization opens voltage-gated calcium channels, producing calcium influx and the final calcium signal that triggers GH exocytosis from secretory granules [13, 14].

A notable feature of GHSR1a is its high constitutive activity: the receptor signals at approximately 50 percent of maximum even in the absence of agonist, a property that may contribute to basal GH tone and that has implications for inverse agonist pharmacology and for receptor desensitization kinetics [14].

4.2 Tabimorelin receptor interaction

Tabimorelin binds the GHSR1a receptor at the orthosteric (ghrelin-binding) site with high affinity. Hansen et al. (1999) reported that NN703 inhibited binding of radiolabeled MK-0677 to human GHSR1a receptors, although the observed K_i value was lower than expected relative to the compound's functional potency [1]. In GHSR1a-expressing cell lines, tabimorelin activated inositol phosphate turnover (a Gq/11-coupled readout) with potency somewhat reduced relative to GHRP-6 and MK-0677 but with comparable efficacy (similar maximal response). The compound is therefore classified as a full agonist at GHSR1a at the level of inositol phosphate signaling.

The functional consequence of GHSR1a activation in anterior pituitary somatotroph cells is the release of preformed growth hormone from secretory granules. The release is pulsatile, reflecting the calcium-dependent exocytotic mechanism. Tabimorelin-induced GH release is additive with, and in some experimental paradigms synergistic with, GHRH-induced GH release, consistent with the established model in which GHRH acts through the Gs-adenylate cyclase-cAMP pathway and GHSR1a agonists act through the Gq-PLC-calcium pathway, and the two pathways converge on the exocytotic machinery through complementary calcium and cAMP signals [13].

4.3 Non-GH hormonal effects

GHSR1a agonists produce variable effects on non-GH hormones depending on their selectivity profile and dose. Tabimorelin at doses producing significant GH release produced transient, modest increases in ACTH, cortisol, and prolactin in both animal models and human subjects [1, 2, 3]. In the swine model, cortisol elevation (50 percent above baseline) was observed at all tested doses in a non-dose-dependent pattern, suggesting either a threshold effect or a mechanism partially distinct from the GHSR1a-GH axis [1]. In healthy human volunteers, single-dose tabimorelin produced no significant cortisol elevation, and the transient prolactin and ACTH increases observed on day 1 of the repeated-dose study resolved by day 7 [2, 3]. This

selectivity profile is intermediate between ipamorelin (which produces essentially no non-GH hormonal perturbation) and the earlier, less selective compounds GHRP-6 and hexarelin (which produce substantial cortisol and prolactin elevation). The selectivity is pharmacologically relevant because chronic cortisol elevation would produce adrenal axis perturbation and metabolic adverse effects, and chronic prolactin elevation would produce galactorrhea and hypogonadism.

4.4 Receptor desensitization and tachyphylaxis

The GH tachyphylaxis observed in the 7-day repeated-dose study (significant decline in GH release from day 1 to day 7, $P < 0.001$) reflects GHSR1a receptor desensitization and/or depletion of the readily releasable pool of GH from pituitary somatotroph cells [3]. GHSR1a, like other G protein-coupled receptors, undergoes agonist-induced phosphorylation, beta-arrestin recruitment, and internalization, producing homologous desensitization on sustained or repeated agonist exposure. The rate and magnitude of desensitization depend on the agonist's intrinsic activity, its dissociation kinetics, and the dosing interval relative to receptor recycling. The tachyphylaxis with daily tabimorelin dosing was sufficient to reduce the magnitude of the GH response by day 7 but did not eliminate it: GH AUC remained significantly above placebo on day 7, indicating that partial receptor repletion occurred during the 24-hour dosing interval [3]. The tachyphylaxis phenomenon is shared across the GHSR1a agonist class and has been observed with ibutamoren and capromorelin on chronic dosing, although the magnitude varies by compound and dosing regimen.

4.5 Downstream physiological effects

The principal downstream physiological effect of sustained GH elevation is hepatic production of IGF-1 and IGFBP-3, the effector arm of the GH-IGF-1 axis. Tabimorelin increased IGF-1 and IGFBP-3 at all dose levels in the 7-day repeated-dose study, with significantly greater IGF-1 elevation at the three highest doses [3]. The IGF-1 elevation is the clinically meaningful endpoint, as the therapeutic rationale for GH secretagogues in adult GH deficiency is to normalize the GH-IGF-1 axis and thereby improve body composition (lean body mass, visceral adiposity), bone mineral density, cardiovascular risk profile, and quality of life.

The GHSR1a receptor in the hypothalamic arcuate nucleus additionally activates orexigenic (appetite-stimulating) neuropeptide Y/agouti-related peptide neurons, and ghrelin receptor activation is one of the principal central signals for meal initi-

ation. Tabimorelin, like other GHSR1a agonists, would be expected to produce appetite stimulation, although this effect was not a primary endpoint in the clinical studies and was not reported as a significant adverse event at the doses tested.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Tabimorelin is absorbed from the gastrointestinal tract after oral administration. Absorption was characterized as nonlinear in the Phase 1 clinical studies: bioavailability increased with dose, consistent with saturation of a first-pass metabolic or efflux process [2]. In beagle dogs, oral bioavailability at the studied dose was approximately 30 percent [1]. In humans, the absorption was sufficiently rapid and complete to produce pharmacodynamically active plasma concentrations (dose-dependent GH release) at doses of 1.5 mg/kg and above. The serum concentration of NN703 required for half-maximal stimulation of GH release was estimated at 485 ng/mL by pharmacokinetic-pharmacodynamic modeling [15].

Time to peak plasma concentration after oral administration was not reported in the published single-dose study abstract but was characterized in the pharmacokinetic-pharmacodynamic modeling study of Agersoe et al. (2001), which employed a two-compartmental model with zero-order input to describe the pharmacokinetics of NN703 in healthy volunteers [15].

5.2 Distribution

In beagle dogs, the volume of distribution was consistent with moderate tissue partitioning. Plasma protein binding has not been reported in detail in the published literature. The compound's molecular weight (528.70 daltons) and lipophilicity are consistent with distribution into peripheral tissues including muscle and adipose tissue. Central nervous system penetration has not been directly characterized in human subjects, although the hypothalamic and pituitary effects of the compound are consistent with either blood-brain barrier penetration or action at circumventricular organs (the median eminence and the area postrema are outside the blood-brain barrier).

5.3 Metabolism

Tabimorelin is metabolized hepatically. The compound is a substrate of cytochrome P450 enzymes, with CYP3A4 identified as the principal metabolic isoform. The Zdravkovic et al. (2003) clinical pharmacology study established that tabimorelin is a mechanism-based (irreversible) inhibitor of CYP3A4, based on in vitro human liver microsome data and confirmed by in vivo drug-drug interaction studies with midazolam [5].

Mechanism-based inhibition (also termed time-dependent or suicide inhibition) involves the CYP3A4-catalyzed formation of a reactive metabolite of tabimorelin that covalently modifies the CYP3A4 active site, permanently inactivating the enzyme molecule. Recovery of CYP3A4 activity therefore requires de novo enzyme synthesis, a process with a half-life of approximately 2 to 3 days. This mechanism explains the persistent elevation of midazolam AUC (45 percent above baseline) observed 7 days after the last tabimorelin dose, a finding inconsistent with reversible competitive inhibition and diagnostic of the mechanism-based process [5].

The single-dose midazolam AUC increase of 64 percent and the repeated-dose increase of 93 percent classify the interaction as moderate to strong by current regulatory guidance (FDA and EMA define a strong CYP3A4 inhibitor as one producing a 5-fold or greater increase in sensitive substrate AUC, and a moderate inhibitor as a 2- to 5-fold increase; tabimorelin's approximately 2-fold increase at steady state places it at the moderate-to-strong boundary). The alpha-hydroxymidazolam AUC increased by 34 percent after a single dose, further confirming the CYP3A4-mediated mechanism [5].

5.4 Elimination

In beagle dogs, the plasma elimination half-life was 4.1 plus or minus 0.4 hours after intravenous administration [1]. Human elimination pharmacokinetics were characterized by the two-compartmental model of Agersoe et al. (2001) [15]. The compound is cleared through hepatic metabolism, with renal excretion of unchanged drug expected to be a minor pathway based on the molecular weight and lipophilicity.

5.5 Routes of administration

Tabimorelin was developed and clinically evaluated exclusively as an oral formulation, reflecting the program's objective of providing a non-injectable alternative to recombinant GH. The compound was administered as a capsule or oral solution in clinical studies. Parenteral (intravenous, subcutaneous) administration was used in preclinical animal studies for pharmacokinetic and pharmacodynamic characterization but was not advanced to human clinical use.

5.6 Special populations

Pharmacokinetic characterization in special populations (renal impairment, hepatic impairment, pediatric, geriatric) was not performed, as development was discontinued before these studies would have been conducted. The CYP3A4 mechanism-based inhibition would predict substantially altered pharmacokinetics and increased drug-drug interaction risk in patients with hepatic impairment, where CYP3A4 activity is already reduced.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

In rat anterior pituitary cell cultures, tabimorelin stimulated GH release in a dose-dependent manner with potency and efficacy similar to GHRP-6, the reference growth hormone-releasing peptide [1]. The compound activated inositol phosphate turnover in GHSR1a-expressing cell lines, confirming the Gq/11-coupled signaling mechanism. Binding studies using radiolabeled MK-0677 displacement demonstrated high-affinity GHSR1a binding, although the K_i was somewhat lower than predicted from functional potency, a discrepancy that may reflect differences in assay conditions or receptor reserve between binding and functional assays [1].

6.2 In vivo pharmacology in swine

Intravenous NN703 in swine produced dose-dependent GH release with a potency (ED₅₀) of 155 plus or minus 23 nmol/kg and a maximum GH response of 91 plus or minus 7 ng/mL plasma [1]. Cortisol elevation (approximately 50 percent above baseline) was observed at all tested doses in a non-dose-dependent pattern. The cortisol finding was noted as a potential concern but was interpreted as pharmacologically manageable given the non-dose-dependent character and the absence of cortisol elevation in subsequent human studies at clinically relevant doses [1, 2].

6.3 In vivo pharmacology in dogs

Oral administration of NN703 to beagle dogs produced dose-dependent GH release. At the highest tested dose (20 micromol/kg), peak GH concentration increased 35-fold to 49.5 plus or minus 17.8 ng/mL [1]. Intravenous administration at 1 micromol/kg produced a peak of 38.5 plus or minus 19.6 ng/mL at approximately 30 minutes. Comparison of oral and intravenous pharmacokinetics yielded an oral bioavailability estimate of approximately 30 percent and a plasma elimination half-life of 4.1 plus or minus 0.4 hours [1]. These pharmacokinetic parameters supported advancement to human clinical evaluation.

6.4 Chronic dosing in rats

Oral NN703 at 100 micromol/kg once daily for 14 days produced significantly greater body weight gain in rats compared to vehicle-treated controls [1]. The increased body weight gain was consistent with sustained GH-IGF-1 axis stimulation producing anabolic effects on lean tissue mass. Detailed body composition analysis (lean mass versus fat mass partitioning) was not reported in the primary publication. The chronic dosing study demonstrated that the compound retained biological activity on repeated administration, although the magnitude of the GH response per dose was not reported across the 14-day period and the tachyphylaxis phenomenon observed in human studies may have been present.

6.5 Structure-activity relationships

The Novo Nordisk medicinal chemistry program produced extensive structure-activity relationship data for the peptidomimetic GH secretagogue class. Key findings included the essential role of the D-2-naphthylalanine pharmacophore for GHSR1a binding (consistent with the known binding pose of ghrelin mimetics in the GHSR1a orthosteric site), the importance of the D-configuration at both chiral centers for receptor selectivity, and the beneficial effect of backbone N-methylation on oral bioavailability without loss of in vivo potency [6, 7]. Subsequent hybrid compounds incorporating C-terminal extensions from ipamorelin onto the NN703 scaffold achieved EC₅₀ values in the low nanomolar range in vitro and oral bioavailabilities of approximately 40 percent, although none were advanced clinically [8, 9].

7. Clinical Evidence Base

7.1 Phase 1 single-dose ascending study

The first-in-human study (Zdravkovic et al. 2000) was a double-blind, randomized, placebo-controlled, single-dose ascending study in healthy male volunteers at eight dose levels from 0.05 to 12 mg/kg body weight [2]. The primary endpoints were safety, tolerability, pharmacokinetics, and pharmacodynamic GH response.

GH AUC (0 to 24 hours) was significantly higher than placebo at 3.0 mg/kg ($P = 0.027$), 6.0 mg/kg ($P = 0.0023$), and 12 mg/kg ($P < 0.0001$). GH peak concentration was significantly elevated at 1.5, 3.0, 6.0, and 12 mg/kg. IGF-1 was significantly elevated at the two highest dose levels (6.0 and 12.0 mg/kg, $P < 0.0001$). No significant increases in ACTH, LH, FSH, TSH, prolactin, or cortisol were observed at the four highest doses, although subtle individual increases in ACTH, cortisol, and prolactin were noted above 3.0 mg/kg [2]. The compound was well tolerated with no serious adverse events.

7.2 Phase 1 repeated-dose study

The repeated-dose study (Zdravkovic et al. 2000) was a randomized, double-blind, placebo-controlled evaluation of 7 days of once-daily oral NN703 at four dose levels (1.71, 3.0, 4.5, and 6.86 mg/kg) in healthy male subjects [3].

GH AUC (0 to 12 hours) and GH Cmax showed dose-related increases that were significantly above placebo on both days 1 and 7 ($P = 0.04$ to $P < 0.0001$). However, an overall significant decrease in GH release from day 1 to day 7 ($P < 0.001$) demonstrated tachyphylaxis at the somatotroph level [3].

IGF-1 and IGFBP-3 increased at all dose levels; IGF-1 elevation was significantly above placebo at the three highest doses. The IGF-1 increase was sustained through day 7, indicating that despite the attenuation of the acute GH secretory response, the cumulative GH exposure was sufficient to drive hepatic IGF-1 production.

No significant increases in FSH, LH, or cortisol were observed on either day 1 or day 7. On day 1 only, significant increases in prolactin (at 1.71 and 6.86 mg/kg, $P < 0.05$), TSH, and ACTH were found at certain dose levels; these resolved by day 7,

with a significant decrease in ACTH and cortisol observed on day 7 [3].

7.3 Phase 2 study in adult growth hormone deficiency

The pivotal efficacy study (Svensson et al. 2003) was a multicentre, randomized, double-blind, placebo-controlled trial in 97 adults with confirmed growth hormone deficiency [4]. Patients received oral NN703 (n = 83) or placebo (n = 14) for 1 week, with the first and final doses at 3 mg/kg and intermediate doses at 1.5 mg/kg daily. All patients additionally received 1 microgram/kg GHRH three weeks post-treatment as a reference stimulus.

Nine of 83 NN703-treated patients (11 percent) achieved a serum peak GH concentration of 5 micrograms per liter or greater after the first and/or final NN703 dose, compared to zero of 14 placebo patients. Serum GH peak and AUC after the first NN703 dose were greater than placebo ($P < 0.05$), but this difference lost statistical significance after correction for lower body mass index in the NN703 group [4].

Serum IGF-1 was unaffected by 1-week NN703 treatment. Serum IGFBP-3 was modestly increased ($P < 0.05$ versus placebo). The mean peak GH after GHRH was 2.1 micrograms per liter, compared to 1.32 micrograms per liter after the initial NN703 dose, indicating that residual somatotroph capacity (as measured by GHRH responsiveness) was the principal determinant of NN703 response.

The investigators concluded that although a majority of GH-deficient adults would not respond to NN703, the compound could potentially be useful in some patients with moderately severe GH deficiency who retained residual pituitary function [4]. The compound was generally well tolerated in this population.

7.4 CYP3A4 interaction study

The drug-drug interaction study (Zdravkovic et al. 2003) evaluated the effect of NN703 on the pharmacokinetics of oral midazolam (7.5 mg), a sensitive CYP3A4 substrate, in 17 adult male subjects [5]. Midazolam was administered at four time-points: baseline, after a single NN703 dose, after 7 days of daily NN703, and after a 7-day washout.

After a single NN703 dose, midazolam AUC increased by 64 percent and alpha-hydroxymidazolam AUC increased by 34 percent ($P = 0.0001$ for both). After 7 days of repeated NN703 dosing, midazolam AUC further increased to 93 percent above

baseline. After the 7-day washout, midazolam AUC remained 45 percent higher than baseline [5].

The persistent inhibition after washout is the hallmark of mechanism-based CYP3A4 inhibition: the irreversible inactivation of CYP3A4 enzyme molecules by a reactive tabimorelin metabolite means that recovery requires de novo CYP3A4 protein synthesis, with a functional recovery half-life of approximately 2 to 3 days. The clinical implication is that tabimorelin would produce significant drug-drug interactions with a substantial fraction of concurrently administered medications, including statins (simvastatin, atorvastatin, lovastatin), immunosuppressants (cyclosporine, tacrolimus, sirolimus), calcium channel blockers (nifedipine, felodipine, amlodipine), protease inhibitors, benzodiazepines (midazolam, triazolam, alprazolam), and many others metabolized by CYP3A4.

8. Sourcing and Quality Verification

Tabimorelin is not marketed as a registered pharmaceutical in any jurisdiction. The compound is available exclusively as a research-grade material from multiple chemical and pharmaceutical research suppliers, including MedChemExpress, Cayman Chemical, Tocris, BocSci, MedKoo, and Biosynth. Supply is in milligram to gram quantities as the free base or as the hemifumarate salt. Pricing is moderate, consistent with non-proprietary peptidomimetic compounds of intermediate synthetic complexity, typically in the range of \$100 to \$500 per 100 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 (HPLC) area-percent purity, ideally greater than 95 percent (greater than 98 percent for receptor pharmacology studies where dose-response precision is critical)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 529.32 for the protonated free base)
- Nuclear magnetic resonance spectroscopy (1H -NMR and ^{13}C -NMR) confirmation of structure and stereochemistry against published spectral data
- Chiral chromatography confirmation of stereochemical integrity at both D-amino acid centers
- Residual solvent analysis by gas chromatography for common synthesis solvents (dimethylformamide, dichloromethane, methanol, ethyl acetate, trifluoroacetic acid)
- Karl Fischer or thermogravimetric analysis for water content

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade tabimorelin market is small but established; lot-to-lot variability in purity and stereochemical integrity is possible, and analytical confirmation is appropriate for any investigation where pharmacological precision is important.

Investigators should note that the hemifumarate salt has a different molecular weight than the free base and should adjust molar dose calculations accordingly.

9. Reconstitution and Handling

Tabimorelin is supplied as a lyophilized powder or crystalline solid. The free base has limited aqueous solubility at neutral pH; the hemifumarate salt provides improved solubility for formulation purposes.

For in vitro studies, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO), with working dilutions in assay buffer. The final DMSO concentration in cell-based assays should be maintained below 0.1 to 0.5 percent to avoid solvent effects on GHSR1a-expressing cells. The compound is stable in DMSO stock solutions stored at minus 20 degrees Celsius for at least 6 months; repeated freeze-thaw cycles should be minimized by aliquoting stock solutions at the time of preparation.

For in vivo studies, the compound can be dissolved in saline with addition of a small volume of DMSO (typically 5 to 10 percent) or in aqueous vehicles with pH adjustment (dilute hydrochloric acid to approximately pH 3 to 4) to enhance solubility. Oral dosing solutions and gavage formulations should be prepared fresh or stored refrigerated (2 to 8 degrees Celsius) for no more than 48 hours.

Long-term storage of the solid compound should be at minus 20 degrees Celsius in desiccated, light-protected conditions. The compound is not known to be photosensitive, but light protection is reasonable practice for extended storage. Stability data for the solid under recommended storage conditions indicate stability for at least 2 years.

The compound should be handled with standard laboratory precautions for pharmacologically active research chemicals. Although tabimorelin is not classified as acutely toxic at research quantities, it is a potent GHSR1a agonist and should be treated as pharmacologically active material with respect to accidental exposure.

10. Stack Interactions and Combinations

Tabimorelin interacts with several drug classes through its CYP3A4 mechanism-based inhibition and through its GHSR1a agonist pharmacology. Investigators conducting research with tabimorelin, especially in chronic dosing regimens or in combination with other research compounds, should consider:

CYP3A4 substrates: The mechanism-based CYP3A4 inhibition is the most significant interaction liability. Concurrent administration of tabimorelin with CYP3A4 substrates will increase the substrate's plasma exposure by approximately 2-fold at steady state, with persistent elevation for several days after tabimorelin discontinuation [5]. This interaction is clinically significant for narrow-therapeutic-index CYP3A4 substrates including immunosuppressants (cyclosporine, tacrolimus), anti-coagulants, antiarrhythmics, and certain chemotherapeutic agents.

Other CYP3A4 inhibitors: Concurrent administration with other CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, grapefruit juice) will increase tabimorelin exposure and may produce supra-pharmacological GHSR1a activation with correspondingly increased adverse-event risk.

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) may reduce tabimorelin plasma concentrations and diminish the GH secretory response. However, the mechanism-based CYP3A4 inhibition by tabimorelin may partially offset the induction effect through irreversible enzyme inactivation.

Other GHSR1a agonists: Concurrent use with other ghrelin receptor agonists (ibutamoren, anamorelin, ipamorelin, GHRP-6, GHRP-2, hexarelin) is pharmacologically redundant and would be expected to produce additive receptor desensitization and tachyphylaxis. The combination has not been studied and is not recommended except for receptor pharmacology research purposes where additive or competitive effects are the experimental endpoint.

GHRH analogs: GHRH and GHRH analogs (sermorelin, tesamorelin) act through the GHRH receptor (a Gs-coupled receptor distinct from GHSR1a) and produce synergistic GH release when combined with GHSR1a agonists. This synergy has been demonstrated for other GHSR1a agonists (GHRP-6, ipamorelin) and would be predicted for tabimorelin, although the combination has not been clinically studied with this specific compound.

Somatostatin and somatostatin analogs: Somatostatin (and its synthetic analogs octreotide, lanreotide, pasireotide) inhibits GH release from somatotroph cells and acts as a physiological antagonist of the GH secretagogue response. Concurrent administration would substantially reduce the GH response to tabimorelin.

Glucocorticoids: Chronic glucocorticoid excess suppresses the GH-IGF-1 axis at multiple levels (hypothalamic, pituitary, and hepatic). Concurrent glucocorticoid therapy may reduce the GH response to tabimorelin and may confound IGF-1 endpoint interpretation.

Insulin and insulin sensitizers: GHSR1a activation produces complex effects on glucose homeostasis, including acute hyperglycemia (through GH-mediated insulin resistance) and longer-term insulin resistance on chronic GH elevation. Concurrent insulin or insulin-sensitizer therapy may require dose adjustment.

11. Adverse Events and Safety

11.1 Common adverse events

The Phase 1 and Phase 2 clinical studies reported that tabimorelin was generally well tolerated at the tested doses. Specific adverse-event rates were not enumerated in the published abstracts with the granularity available for marketed compounds, but the following adverse-event categories were noted:

- Gastrointestinal effects (nausea, abdominal discomfort): reported at higher doses, consistent with the gastrointestinal distribution of GHSR1a receptors and the appetite-stimulating mechanism of ghrelin agonism
- Transient increases in prolactin: observed on day 1 at certain dose levels in the repeated-dose study; resolved by day 7
- Transient increases in ACTH: observed on day 1; resolved by day 7
- Appetite stimulation: anticipated from the mechanism (GHSR1a-mediated orexigenic signaling) but not reported as a formal adverse event in the published clinical data

11.2 Hormonal perturbation

The non-GH hormonal effects of tabimorelin represent a potential safety concern for chronic dosing. The transient day-1 elevations in prolactin and ACTH resolved by day 7, suggesting rapid adaptation of these axes [3]. Cortisol was not significantly elevated in human subjects at any dose level on either day 1 or day 7, a favorable finding relative to less selective GHSR1a agonists. The cortisol elevation observed in swine (50 percent above baseline) was not replicated in humans, suggesting species-specific differences in the GHSR1a-hypothalamic-pituitary-adrenal axis coupling [1].

11.3 CYP3A4 inhibition as a safety signal

The mechanism-based CYP3A4 inhibition is the most significant safety concern for chronic tabimorelin use. The irreversible nature of the inhibition means that drug-drug interactions persist for days after compound discontinuation, and the breadth

of the CYP3A4 substrate list means that a substantial fraction of concurrently administered medications would be affected. This finding was a principal factor in the decision to discontinue clinical development [5].

11.4 GH-related safety considerations

Chronic GH elevation, whether from exogenous GH administration or from secretagogue-driven endogenous release, produces known long-term safety concerns including insulin resistance, glucose intolerance, fluid retention, carpal tunnel syndrome, arthralgia, and theoretical concerns about acceleration of neoplastic growth in predisposed individuals. These long-term GH-related risks were not evaluated in the short-duration clinical studies of tabimorelin (maximum 1 week) and would be relevant considerations for any hypothetical chronic dosing regimen.

11.5 Pregnancy and lactation

No human pregnancy or lactation data are available for tabimorelin. Animal reproductive and developmental toxicology data have not been published. The compound's GH-stimulating and appetite-stimulating mechanisms produce theoretical concerns for fetal growth and metabolic programming, and use in pregnant or lactating subjects is not recommended.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five growth hormone secretagogue receptor agonists against tabimorelin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or in vitro), and overall validation. The five comparators were selected as the principal GHSR1a agonists with substantive clinical or preclinical pharmacology programs, with priority on compounds that have produced material clinical evidence or regulatory registration.

12.1 Ibutamoren (MK-0677)

Mechanism: Non-peptide, orally active GHSR1a agonist. Structurally unrelated to tabimorelin; ibutamoren is a spiro-indanylpiperidine derivative developed by Merck Research Laboratories [16]. Full agonist at GHSR1a with oral bioavailability and a long biological half-life permitting once-daily dosing at 25 mg.

Development trajectory: Merck advanced ibutamoren through extensive Phase 2 clinical evaluation in multiple indications including adult growth hormone deficiency, hip fracture recovery, age-related muscle wasting, and obesity. Multiple Phase 2 studies demonstrated sustained elevation of GH, IGF-1, and IGFBP-3 over periods of up to 2 years [16, 17]. The compound increased lean body mass and reduced visceral adiposity in some studies. Despite promising Phase 2 data, Merck did not advance ibutamoren to Phase 3 registration for any indication.

Novelty: Moderate. Ibutamoren was the first non-peptide, orally active GHSR1a agonist and remains the best-characterized compound in the class.

Effect size: Moderate to substantial. One year of ibutamoren therapy at 25 mg daily in older adults increased IGF-1 to levels observed in young adults, increased lean body mass by approximately 1.0 to 1.5 kg, and produced sustained GH elevation, although GH tachyphylaxis was observed on chronic dosing with some attenuation of the acute GH response [17].

Promising potential: Moderate. The compound is not in active commercial development but remains widely available as a research compound and is the subject of continued clinical investigation in academic settings (hemodialysis, sarcopenia, growth retardation). Ibutamoren is widely used in the research peptide and performance-enhancement communities despite lacking regulatory approval.

Side-effect profile: The principal adverse events in clinical trials were increased appetite, weight gain (including fat mass in some studies), transient edema, muscle pain, and elevated fasting glucose. Chronic dosing for 12 to 24 months produced modest increases in fasting glucose and insulin consistent with GH-mediated insulin resistance [17]. The compound does not produce mechanism-based CYP3A4 inhibition, a significant advantage over tabimorelin.

Overall validation: Moderate to high. Ibutamoren has the most extensive clinical pharmacology database of any GHSR1a agonist, spanning multiple indications and treatment durations. The absence of Phase 3 registration limits its formal validation.

Comparison to tabimorelin: Ibutamoren is substantially more clinically advanced than tabimorelin, with larger and longer clinical trials, greater effect sizes on IGF-1 and body composition endpoints, and the absence of the CYP3A4 liability. Tabimorelin's principal advantage over ibutamoren in the research context is its peptidomimetic structure, which provides complementary structure-activity information for GHSR1a medicinal chemistry.

12.2 Anamorelin (ONO-7643, RC-1291)

Mechanism: Orally active, non-peptide GHSR1a agonist. Full agonist at the ghrelin receptor with GH-releasing, appetite-stimulating, and anti-cachectic activity [18].

Development trajectory: Helsinn Healthcare and Ono Pharmaceutical advanced anamorelin through Phase 3 clinical trials for cancer-related anorexia-cachexia-wasting syndrome. The ROMANA 1 and ROMANA 2 pivotal Phase 3 studies (Temel et al. 2016) demonstrated significant improvements in lean body mass and body weight in patients with advanced non-small cell lung cancer, although the co-primary endpoint of handgrip strength was not met [18]. Anamorelin was approved in Japan in 2021 for cancer cachexia (Adlumiz). It has not been approved by the FDA or EMA.

Novelty: Moderate. The cancer cachexia indication is distinct from the GH deficiency indication pursued by tabimorelin.

Effect size: Moderate. Phase 3 trials demonstrated approximately 1.0 to 1.5 kg lean body mass increase over 12 weeks versus placebo, with significant improvement in appetite and body weight. The failure to improve handgrip strength limited the clinical impact [18].

Promising potential: High. Anamorelin is the only GHSR1a agonist approved for a therapeutic indication (cancer cachexia in Japan) and remains in regulatory evaluation for additional jurisdictions.

Side-effect profile: Favorable. Principal adverse events were hyperglycemia, nausea, and peripheral edema, all at modest rates. The compound does not produce mechanism-based CYP3A4 inhibition.

Overall validation: High. Phase 3 registration with regulatory approval in one jurisdiction represents the highest validation level in the GHSR1a agonist class.

Comparison to tabimorelin: Anamorelin is substantially more validated than tabimorelin, with Phase 3 data and regulatory approval. The two compounds target different clinical populations (cachexia versus GH deficiency). Tabimorelin's value relative to anamorelin is principally as a peptidomimetic structural reference for medicinal chemistry research.

12.3 Macimorelin (AEZS-130)

Mechanism: Orally active, non-peptide GHSR1a agonist. The compound stimulates GH release and is used as a diagnostic tool rather than a therapeutic agent [19].

Development trajectory: Aeterna Zentaris developed macimorelin as an oral GH stimulation test for the diagnosis of adult growth hormone deficiency. A single oral dose of 0.5 mg/kg produces a GH peak that is interpreted against a diagnostic threshold to confirm or exclude GH deficiency. The pivotal registration study demonstrated 92 percent sensitivity and 96 percent specificity compared to the insulin tolerance test reference standard [19]. Macimorelin was approved by the FDA in 2017 (Macrilen) and by the EMA in 2019, making it the first orally active GHSR1a agonist approved by the FDA and the second approved GHSR1a agonist globally.

Novelty: High for the diagnostic application; the use of a GHSR1a agonist as a diagnostic provocation test rather than a therapeutic agent represents a distinct pharmacological strategy.

Effect size: High for the diagnostic application (92 percent sensitivity, 96 percent specificity). Not applicable as a therapeutic comparator.

Promising potential: Established. Macimorelin is a marketed diagnostic agent with regulatory approval in the United States and the European Union.

Side-effect profile: Favorable for single-dose diagnostic use. Principal adverse events on single-dose administration are dysgeusia (taste disturbance), headache, dizziness, and nausea, all at modest rates and self-limiting. Chronic dosing safety has not been evaluated.

Overall validation: High for the diagnostic indication.

Comparison to tabimorelin: Macimorelin and tabimorelin share the GHSR1a agonist mechanism but occupy entirely different clinical positions (diagnostic versus therapeutic). Macimorelin's FDA approval validates the GHSR1a agonist mechanism for producing acute GH release in humans but does not address the chronic-dosing therapeutic question that was the focus of tabimorelin development.

12.4 Capromorelin (CP-424391)

Mechanism: Orally active, non-peptide GHSR1a agonist with GH-releasing and appetite-stimulating activity.

Development trajectory: Pfizer developed capromorelin originally for human frailty and age-related muscle wasting. Phase 2 clinical studies in elderly subjects demonstrated increased GH and IGF-1, with functional improvements including increased stair climb power and tandem walking speed [20]. However, development for human indications was not advanced to Phase 3. The compound was subsequently developed by Aratana Therapeutics for veterinary use and was approved by the FDA Center for Veterinary Medicine in 2016 (Entyce) for appetite stimulation in dogs and in 2020 (Elura) for weight management in cats.

Novelty: Moderate. The veterinary registration represents a novel application pathway for GHSR1a agonists.

Effect size: Moderate in human Phase 2 studies. Functional improvements (stair climb power, tandem walking) were observed in some but not all measures. IGF-1 elevation required higher or more frequent dosing than ibutamoren to sustain [20].

Promising potential: Limited for human therapeutic use (development discontinued). Established for veterinary use (FDA-approved for dogs and cats).

Side-effect profile: Favorable in human Phase 2 studies. The compound does not produce mechanism-based CYP3A4 inhibition.

Overall validation: Moderate (human Phase 2 data, veterinary regulatory approval).

Comparison to tabimorelin: Capromorelin advanced further in human clinical evaluation than tabimorelin (Phase 2 with functional endpoints versus Phase 2 with limited GH response) and achieved veterinary regulatory approval, providing a translational validation that tabimorelin lacks. Tabimorelin's peptidomimetic structure provides distinct structure-activity information.

12.5 Ipamorelin (NNC 26-0161)

Mechanism: Pentapeptide GHSR1a agonist. The most selective growth hormone secretagogue in the peptide class, ipamorelin stimulates GH release without producing significant increases in ACTH, cortisol, or prolactin, a selectivity that distinguishes it from GHRP-6, GHRP-2, and hexarelin [10].

Development trajectory: Novo Nordisk developed ipamorelin as an injectable GH secretagogue. The compound was evaluated in Phase 2 clinical studies for multiple indications. Ipamorelin was not advanced to registration by Novo Nordisk. The compound is widely available as a research-grade peptide and is extensively used in the research peptide community.

Novelty: Moderate. Ipamorelin was the first selective GH secretagogue and demonstrated that GH-axis selectivity could be achieved within the GHSR1a agonist class [10].

Effect size: Moderate. Ipamorelin produces robust, dose-dependent GH release with excellent GH selectivity (no cortisol, no prolactin elevation) in both animal and human studies.

Promising potential: Limited as a registered therapeutic. Substantial as a research tool and reference compound.

Side-effect profile: Favorable. The GH selectivity of ipamorelin (no cortisol, no prolactin elevation) represents the best selectivity profile in the GHSR1a agonist class. The compound does not produce CYP3A4 inhibition (as a pentapeptide, it is not hepatically metabolized by CYP enzymes). The principal limitation is the absence of oral bioavailability, requiring parenteral administration.

Overall validation: Moderate. Extensive preclinical and Phase 2 clinical data; not advanced to registration.

Comparison to tabimorelin: Ipamorelin is the direct structural parent of tabimorelin. The key differences are that ipamorelin requires parenteral administration (no oral bioavailability) but has superior GH selectivity (no cortisol or prolactin effects) and no CYP3A4 liability, while tabimorelin has oral bioavailability but reduced GH selectivity and clinically significant CYP3A4 inhibition. The comparison illustrates the trade-off between oral bioavailability (requiring backbone reduction and lipophilicity optimization) and selectivity/safety (which was compromised in the optimization process).

12.6 Comparator summary

The five comparators occupy distinct positions in the GHSR1a agonist landscape. **Ibutamoren** is the most extensively studied non-peptide GHSR1a agonist with the largest clinical database, demonstrating sustained IGF-1 elevation and body composition effects over treatment periods of up to 2 years, but lacking regulatory approval. **Anamorelin** is the most clinically validated, with Phase 3 data and regulatory approval in Japan for cancer cachexia. **Macimorelin** achieved FDA and EMA approval as a diagnostic agent, validating the GHSR1a mechanism for acute GH provocation but not for chronic therapeutic use. **Capromorelin** achieved veterinary regulatory approval and demonstrated functional improvements in elderly humans at Phase 2 but was not advanced for human registration. **Ipamorelin** is the direct structural parent of tabimorelin and the selectivity benchmark for the class, with robust GH release without cortisol or prolactin perturbation but no oral bioavailability.

Tabimorelin occupies a unique but limited position in this landscape: it is the only peptidomimetic (backbone-reduced peptide derivative) GHSR1a agonist advanced to human clinical evaluation, and it provides the critical translational data linking the ipamorelin peptide pharmacology to oral small-molecule drug development. However, the compound's clinical development was terminated by three converging liabilities: modest efficacy in the GH-deficient target population (reflecting the fundamental limitation of the secretagogue mechanism in severe pituitary disease), GH tachyphylaxis on repeated dosing (a class effect), and mechanism-based CYP3A4 inhibition (a compound-specific liability). The CYP3A4 inhibition is notably absent from the comparator compounds (ibutamoren, anamorelin, macimorelin, capromorelin, and ipamorelin), suggesting that it is a structural property of the tabimorelin peptidomimetic scaffold rather than an intrinsic consequence of GHSR1a agonism.

The practical research value of tabimorelin in the current landscape is principally as a medicinal chemistry reference compound for peptidomimetic GHSR1a agonist development, as a pharmacological tool for GHSR1a receptor characterization in vitro, and as a historical case study in the challenges of optimizing peptide leads for oral bioavailability while maintaining selectivity and metabolic safety. Investigators considering GHSR1a agonists for GH-IGF-1 axis research would generally prefer ibutamoren (oral, non-peptide, no CYP3A4 liability, extensive clinical database) or ipamorelin (injectable, selective, no CYP3A4 liability) over tabimorelin for most applications.

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