

RESEARCH MONOGRAPH . COMPOUND PROFILE

Capromorelin

A non-peptide ghrelin receptor agonist developed at Pfizer as a peptidomimetic growth hormone secretagogue for age-related functional decline, subsequently approved in veterinary medicine for appetite stimulation in dogs and weight management in cats with chronic kidney disease.

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ABSTRACT

Capromorelin (CP-424,391) is an orally active, non-peptide agonist of the growth hormone secretagogue receptor type 1a (GHS-R1a, the ghrelin receptor) belonging to the pyrazolinone-piperidine dipeptide structural class. The compound was discovered at Pfizer Global Research and Development through systematic structure-activity optimization of peptidomimetic scaffolds and was selected as a clinical development candidate on the basis of high receptor affinity ($K_i = 7$ nM at human GHS-R1a), potent functional activity ($EC_{50} = 3$ nM in rat pituicyte growth hormone release assay), oral bioavailability, and robust in vivo growth hormone secretion in rodent and canine models [1, 2]. Capromorelin mimics the endogenous acylated peptide hormone ghrelin by binding the GHS-R1a receptor on somatotroph cells of the anterior pituitary gland and on hypothalamic neurons, activating Gq/11-coupled phospholipase C signaling, intracellular calcium mobilization, and consequent pulsatile growth hormone release through a pathway mechanistically distinct from and synergistic with the growth hormone releasing hormone (GHRH) receptor pathway. Secondary pharmacological activities include appetite stimulation through hypothalamic orexigenic circuits, transient elevation of circulating cortisol and prolactin, and sustained elevation of insulin-like growth factor 1 (IGF-1) on chronic dosing. In human clinical development, capromorelin advanced through Phase I single ascending dose studies in healthy volunteers and spinal cord injured patients (Ellis et al. 2015), demonstrating safety, tolerability, and dose-proportional pharmacokinetics at oral doses of 20 to 100 mg, and through a Phase II multicenter randomized placebo-controlled trial in 395

older adults aged 65 to 84 years with mild functional limitation (White et al. 2009), in which 12 months of daily oral capromorelin produced statistically significant increases in lean body mass (1.4 kg at 6 months, 1.6 kg at 12 months), growth hormone secretion, IGF-1 concentrations, and tandem stair climbing power compared to placebo [5, 6]. Human clinical development was subsequently discontinued; the compound did not advance to Phase III registration trials for age-related sarcopenia or functional decline. In veterinary medicine, capromorelin oral solution received United States Food and Drug Administration approval in 2016 as Entyce (Aratana Therapeutics, subsequently Elanco Animal Health) for appetite stimulation in dogs at an oral dose of 3 mg/kg once daily, and in October 2020 as Elura for the management of weight loss in cats with chronic kidney disease [7, 8, 9]. These veterinary approvals represent the only registered therapeutic applications of capromorelin as of the most recent monograph revision. The compound is the first and only FDA-approved ghrelin receptor agonist for appetite stimulation in companion animals and demonstrates the translational validity of the GHS-R1a mechanism for orexigenic and anabolic applications. Pharmacokinetics in dogs are characterized by rapid oral absorption (T_{max} approximately 0.83 hours), moderate oral bioavailability (44 percent), hepatic metabolism predominantly through CYP3A4 and CYP3A5 mediated N-dealkylation and O-debenzylation, and a short terminal elimination half-life (approximately 1.2 hours in dogs, 2.4 hours in rats) [2, 15, 16]. In humans, single ascending oral doses of 20 to 100 mg produced dose-proportional increases in plasma concentration with broadly similar pharmacokinetic behavior between able-bodied and spinal cord injured participants [5]. The compound is well tolerated at studied doses; the principal adverse events across species are

transient hypersalivation, mild emesis, loose stools, and transient increases in serum cortisol and glucose concentrations that normalize within hours of dosing. This monograph reviews the chemistry, synthesis, and structure-activity relationships of capromorelin; the GHS-R1a receptor pharmacology and downstream signaling; the comprehensive pharmacokinetic record across species; the preclinical pharmacology in rodent and canine models; the human clinical evidence base including Phase I and Phase II trials; the veterinary clinical evidence and regulatory approvals; sourcing and quality verification; reconstitution and handling; stack-interaction considerations for research applications; the adverse-event and safety profile; and a comparative assessment of five growth hormone secretagogue candidates (ibutamoren, anamorelin, macimorelin, ipamorelin, tabimorelin) against capromorelin 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: Capromorelin (proposed; not formally assigned by the World Health Organization as the compound did not reach human registration).

Marketed names: Entyce (Elanco Animal Health; United States, veterinary, dogs), Elura (Elanco Animal Health; United States, veterinary, cats).

Development codes: CP-424,391 (Pfizer Global Research and Development, Groton, Connecticut). The development code CP-424,391 is the canonical identifier in the preclinical and early clinical pharmacology literature. The tartrate salt form used in formulated products is designated CP-424,391-18 in some regulatory documents [1, 2].

Chemical Abstracts Service registry numbers: 193273-66-4 (free base), 193273-69-7 (tartrate salt). The tartrate salt is the pharmaceutical and veterinary formulation form; the free base is the synthetic and reference standard form.

International Union of Pure and Applied Chemistry name: 2-amino-N-[(1R)-2-[(3aR)-2-methyl-3-oxo-3a-(phenylmethyl)-3,3a,4,6,7,7a-hexahydro-2H-pyrazolo[4,3-c]pyridin-5-yl]-1-(1-oxo-2,3-dihydro-1H-inden-5-yl)-2-oxoethyl]propanamide.

PubChem CID: 216208.

1.2 Structural class and chemistry

Capromorelin belongs to the pyrazolinone-piperidine dipeptide class of growth hormone secretagogues, a structural series developed at Pfizer through iterative medicinal chemistry optimization of peptidomimetic scaffolds designed to mimic the pharmacophoric elements of the endogenous hormone ghrelin without the metabolic liability of a peptide backbone [1]. The compound is a non-peptide, small-molecule peptidomimetic that achieves oral bioavailability through resistance to gastrointestinal proteolysis and efficient intestinal absorption. The struc-

tural class is distinct from the spiroindanylpiperidine GHS (exemplified by ibutamoren/MK-677), the benzolactam GHS (exemplified by macimorelin), and the peptidic GHS (exemplified by ipamorelin and GHRP-6).

Molecular formula: C₂₈H₃₅N₅O₄ (free base); C₃₂H₄₁N₅O₈ (tartrate salt).

Molecular weight: 505.62 g/mol (free base); 655.70 g/mol (tartrate salt).

Exact mass: 505.2689 g/mol (free base, monoisotopic).

Physical properties: White to off-white crystalline powder (as the tartrate salt). Soluble in water, methanol, and dimethyl sulfoxide; sparingly soluble in apolar organic solvents. The tartrate salt is the preferred formulation form owing to superior aqueous solubility and crystalline stability.

Stereochemistry: Capomorelin contains two defined stereocenters: the (1R) configuration at the aminoindanone-bearing carbon and the (3aR) configuration at the ring junction of the pyrazolinone-piperidine bicycle. The compound is supplied as the single (1R,3aR) diastereomer. The stereochemical assignment was established during the original medicinal chemistry optimization at Pfizer and confirmed by X-ray crystallography of the tartrate salt [1]. Investigators acquiring research-grade capomorelin should confirm diastereomeric purity by chiral high-performance liquid chromatography.

Key structural features: The molecule comprises four principal pharmacophoric elements: (a) a pyrazolidinone ring providing hydrogen bond donor and acceptor capacity; (b) a piperidine ring conferring conformational rigidity and basic nitrogen character; (c) a benzyl substituent occupying a hydrophobic receptor pocket; and (d) an aminoindanone moiety providing aromatic stacking interactions with the GHS-R1a binding site. The dipeptide-like amide linkage connecting these elements mimics the backbone geometry of ghrelin's N-terminal octanoylated serine-phenylalanine-threonine sequence without incorporating hydrolyzable peptide bonds [1, 2].

1.3 Synthesis

The published synthesis of capomorelin proceeds through construction of the pyrazolinone-piperidine bicyclic core followed by sequential coupling of the benzyl and aminoindanone pharmacophoric elements. Carpino et al. (2003) described the structure-activity optimization that yielded capomorelin as the lead compound

from a series of pyrazolinone-piperidine dipeptide growth hormone secretagogues [1]. The synthetic route involves: (a) construction of the 3a-benzyl-2-methylpyrazolidinone ring system through cyclization of appropriately substituted hydrazine and keto-acid precursors; (b) elaboration of the piperidine nitrogen through reductive amination or acylation; (c) coupling of the aminoindanone fragment through standard peptide coupling chemistry (carbodiimide or uronium-mediated amide bond formation); and (d) resolution or asymmetric synthesis to obtain the (1R,3aR) diastereomer [1, 3]. A practical process-chemistry route employing crystallization-induced dynamic resolution with L-tartaric acid has been developed for scale-up, providing the (3aR) diastereomer in greater than 85 percent chemical yield and approximately 98 percent diastereomeric excess [3]. The tartrate salt is prepared by treatment with L-tartaric acid in an appropriate solvent followed by recrystallization. Industrial synthesis achieves high diastereomeric and enantiomeric purity (greater than 98 percent by chiral HPLC) and is scalable to multi-kilogram quantities for pharmaceutical and veterinary formulation.

2. Abstract

Capromorelin (CP-424,391) is a potent, orally active, non-peptide agonist of the growth hormone secretagogue receptor type 1a (GHS-R1a), the endogenous receptor for the acylated peptide hormone ghrelin, developed at Pfizer Global Research and Development as a clinical candidate for age-related growth hormone decline, sarcopenia, and functional limitation in elderly populations [1, 2]. The compound represents a distinct structural class (pyrazolinone-piperidine dipeptides) from other ghrelin receptor agonists in clinical development and achieves its pharmacological activity through high-affinity binding to GHS-R1a ($K_i = 7$ nM), activation of Gq/11-coupled intracellular calcium signaling in anterior pituitary somatotrophs, and consequent stimulation of pulsatile growth hormone release [2, 4].

The principal human clinical evidence derives from two studies. The Ellis et al. (2015) Phase I single ascending dose trial in 12 healthy able-bodied volunteers and spinal cord injured patients demonstrated safety, tolerability, and dose-proportional pharmacokinetics at oral doses of 20, 50, and 100 mg, with no serious adverse events and with growth hormone stimulation confirmed at all dose levels [5]. The White et al. (2009) Phase II multicenter randomized double-blind placebo-controlled trial in 395 men and women aged 65 to 84 years with mild functional limitation randomized participants to one of four oral capromorelin regimens (10 mg three times weekly, 3 mg twice daily, 10 mg nightly, or 10 mg twice daily) or placebo for an intended 24 months of treatment [6]. At 12 months, all capromorelin groups demonstrated significant increases in lean body mass (mean 1.4 kg at 6 months, 1.6 kg at 12 months), IGF-1 concentrations, and tandem stair climbing power relative to placebo. Total body weight also increased (approximately 1.5 kg), partially offsetting the lean mass gain when expressed as percentage lean mass. The study was terminated early (at 12 months rather than 24 months) due to a Pfizer strategic portfolio decision; the compound did not advance to Phase III [6].

In veterinary medicine, capromorelin oral solution received FDA approval in 2016 for appetite stimulation in dogs (Entyce, 3 mg/kg once daily) and in October 2020 for management of weight loss in cats with chronic kidney disease (Elura, 2 mg/kg once daily) [7, 8, 9]. Pivotal veterinary trials demonstrated significant appetite stimulation and weight gain relative to placebo in both species. The veteri-

nary approvals validate the GHS-R1a agonist mechanism for orexigenic and anabolic applications and provide a substantial safety database across thousands of treated companion animals.

The compound is not approved for human use in any jurisdiction. It is available as a research-grade compound from multiple chemical suppliers and as a veterinary pharmaceutical in its registered formulations. The research-clinical positioning of capromorelin is as a validated GHS-R1a agonist tool compound with demonstrated oral bioactivity, a short duration of action favorable for pulsatile growth hormone physiology research, and a well-characterized safety profile across species.

3. Discovery and Development History

3.1 Origin

Capromorelin was discovered at Pfizer Global Research and Development in Groton, Connecticut, through a medicinal chemistry program directed at identifying orally active, non-peptide growth hormone secretagogues [1, 2]. The program was initiated in the late 1990s following the clinical validation of the growth hormone secretagogue concept by earlier peptide-based agents (growth hormone releasing peptide-6, hexarelin) and by Merck's non-peptide compound MK-677 (ibutamoren), which demonstrated that oral, non-peptide GHS-R1a agonists could produce sustained growth hormone elevation in humans [10]. The 1996 cloning of the growth hormone secretagogue receptor by Howard et al. at Merck Research Laboratories and the 1999 identification of ghrelin as its endogenous ligand by Kojima et al. at the National Cardiovascular Center Research Institute in Osaka provided the molecular target framework for rational drug design [4, 11]. Pfizer's objective was to develop a structurally distinct compound with improved selectivity, shorter duration of action (to preserve physiological pulsatile GH secretion), and a favorable safety profile for chronic dosing in elderly populations.

3.2 Medicinal chemistry optimization

Carpino et al. (2003) reported the discovery of capromorelin from systematic modification of pyrazolinone-piperidine dipeptide scaffolds [1]. The optimization focused on: receptor affinity at GHS-R1a (target K_i below 10 nM); functional potency in rat pituitary GH release assays (target EC_{50} below 10 nM); oral bioavailability in rodent pharmacokinetic models; metabolic stability against hepatic microsomal degradation; and selectivity against off-target receptors. From this series, capromorelin (CP-424,391; hGHS-R1a K_i = 7 nM, rat pituitary EC_{50} = 3 nM) and its desmethyl analogue (compound 5c; hGHS-R1a K_i = 17 nM, rat pituitary EC_{50} = 3 nM) were identified as the lead candidates with oral GH-releasing activity in dogs [1]. Capromorelin was selected as the clinical candidate on the basis of its combined receptor potency, oral bioavailability, and pharmacokinetic profile permitting pulsatile rather than sustained GH stimulation.

3.3 Preclinical development

Pan et al. (2001) published the preclinical pharmacology of CP-424,391 in the journal *Endocrine*, demonstrating: dose-dependent pulsatile GH release in anesthetized rats and conscious dogs following oral administration; activation of intracellular calcium signaling (but not cAMP) in rat pituitary cell cultures; modulation of GH-releasing hormone and somatostatin effects on pituitary GH secretion; rapid oral absorption (Tmax approximately 1 hour in dogs); and wide tissue distribution excluding the central nervous system in radiolabeled pharmacokinetic studies [2]. Kamath et al. (2001) published the metabolism, pharmacokinetics, tissue distribution, and excretion of radiolabeled CP-424,391 in rats in *Drug Metabolism and Disposition*, establishing the hepatic metabolic pathway and the fecal and urinary elimination profile [16]. The preclinical safety pharmacology demonstrated no significant cardiovascular, respiratory, or central nervous system adverse signals at multiples of the anticipated clinical dose.

3.4 Human clinical development

Pfizer advanced capromorelin through Phase I (single ascending dose safety and pharmacokinetics) and Phase II (12-month efficacy in functionally limited elderly adults) clinical programs between approximately 2002 and 2007 [5, 6]. The Phase II study (NCT00527046) was the largest clinical trial of capromorelin in humans and demonstrated efficacy on anabolic endpoints (lean body mass, IGF-1, stair climbing power) but was terminated early at 12 months due to a strategic portfolio decision by Pfizer rather than safety or efficacy concerns. Human development was discontinued; the compound was not advanced to Phase III for any human indication.

3.5 Veterinary development and approval

Aratana Therapeutics acquired rights to capromorelin for veterinary applications and developed the oral solution formulation for companion animal use. The FDA approved Entyce (capromorelin oral solution, 30 mg/mL) in May 2016 for appetite stimulation in dogs, making it the first and only FDA-approved appetite stimulant for dogs [7]. Aratana was subsequently acquired by Elanco Animal Health in 2019. In October 2020, the FDA approved Elura (capromorelin oral solution, 18 mg/mL) for management of weight loss in cats with chronic kidney disease [8]. These veterinary approvals provide a regulatory validation of the GHS-R1a agonist mechanism and a substantial post-approval safety database.

3.6 Continued research interest

A 2025 report in the Journal of Medicinal Chemistry described the design and biological characterization of capromorelin derivatives with extended half-lives as next-generation oral GHS-R1a agonists for growth hormone deficiency, indicating continued medicinal chemistry interest in the capromorelin scaffold [12]. Kumar and Singh (2023) published a comprehensive review of discovery, efficacy, safety, and clinical applications of capromorelin in veterinary medicine in Veterinary Research Communications [13]. These publications indicate sustained research interest in both the compound itself and the broader GHS-R1a pharmacology it exemplifies.

3.7 Current status

As of the most recent monograph revision, capromorelin is: (a) approved and marketed for veterinary use in dogs (Entyce) and cats (Elura) in the United States; (b) not approved for human use in any jurisdiction; (c) not in active human clinical development; (d) available as a research-grade compound from multiple chemical suppliers; and (e) the subject of continued research interest as a tool compound for GHS-R1a receptor pharmacology, appetite physiology, and growth hormone axis investigation.

4. Mechanism of Action

Capromorelin is a selective agonist of the growth hormone secretagogue receptor type 1a (GHS-R1a), a seven-transmembrane-domain G-protein coupled receptor that is the endogenous receptor for the 28-amino-acid acylated peptide hormone ghrelin [4, 11]. The GHS-R1a is expressed at high density on somatotroph cells of the anterior pituitary gland, on neurons of the hypothalamic arcuate nucleus (including neuropeptide Y/agouti-related peptide orexigenic neurons), and at lower density in the hippocampus, ventral tegmental area, nucleus tractus solitarius, and peripheral tissues including the gastrointestinal tract, pancreas, and immune cells [14].

4.1 GHS-R1a receptor binding and activation

Capromorelin binds the orthosteric (ghrelin-binding) site of GHS-R1a with a K_i of 7 nM, as determined by displacement of radiolabeled ligand from membranes expressing human GHS-R1a [1]. The binding affinity places capromorelin among the most potent non-peptide GHS-R1a agonists characterized, comparable to anamorelin ($IC_{50} = 0.69$ nM) and ibutamoren (K_i approximately 1 to 2 nM) [14, 15]. Functional activation in rat pituitary GH release assays demonstrates an EC_{50} of 3 nM, consistent with full agonist activity at the receptor [1, 2].

The GHS-R1a receptor signals predominantly through Gq/11 activation. Upon agonist binding, the receptor activates phospholipase C beta (PLC-beta), generating inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from membrane phosphatidylinositol 4,5-bisphosphate. IP3 stimulates calcium release from endoplasmic reticulum stores, producing intracellular calcium mobilization that triggers growth hormone vesicle exocytosis from somatotroph cells. DAG activates protein kinase C, which inhibits potassium channels, leading to membrane depolarization, opening of voltage-gated calcium channels, and extracellular calcium influx [2, 4, 14]. Pan et al. (2001) confirmed that CP-424,391 activates intracellular calcium signaling but does not elevate intracellular cyclic AMP in rat pituitary cell cultures, consistent with the Gq/11 rather than Gs coupling pathway [2]. The GHS-R1a receptor also couples to additional G-protein subtypes (G α -12/13, G α -i/o) in spe-

cific cellular contexts, mediating cytoskeletal rearrangement and inhibition of adenylyl cyclase, though the Gq/11-PLC-calcium axis is the dominant signaling cascade for GH release [14].

4.2 Distinction from GHRH signaling and synergy

The GHS-R1a signaling pathway (PLC/IP3/calcium) is mechanistically distinct from and complementary to the cAMP-dependent pathway utilized by growth hormone releasing hormone (GHRH) acting through the GHRH receptor on somatotrophs. This mechanistic complementarity means that GHS-R1a agonists and endogenous GHRH produce synergistic rather than merely additive GH release when co-administered [2, 4, 14]. Pan et al. (2001) demonstrated this synergy directly for capromorelin: in rat pituitary cell cultures, co-application of CP-424,391 with GHRH produced GH release exceeding the sum of the individual responses [2]. Capromorelin additionally acts at the hypothalamic level: GHS-R1a receptors on arcuate nucleus neurons stimulate GHRH-releasing neurons while suppressing somatostatin tone, producing a dual amplification of GH secretion at both hypothalamic and pituitary levels [4, 14]. Pan et al. further demonstrated that capromorelin partially overcomes somatostatin-mediated inhibition of GH release, reflecting the ability of the Gq/11-calcium pathway to drive exocytosis independently of the Gi-mediated suppression of cAMP that somatostatin produces through its receptor [2].

4.3 Appetite stimulation

GHS-R1a is expressed at high density on neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus, the principal orexigenic neuronal population. Capromorelin binding to GHS-R1a on these neurons activates NPY/AgRP signaling, stimulates appetite, and increases food intake through the same circuit utilized by endogenous ghrelin [11, 14]. This orexigenic mechanism is the pharmacological basis for the veterinary appetite stimulation indication and is mediated independently of the growth hormone releasing activity. In dogs, oral capromorelin at 3 mg/kg produces measurable appetite stimulation within 30 to 60 minutes of dosing, correlating with the rapid plasma absorption kinetics [7, 9].

4.4 Secondary endocrine effects

GHS-R1a activation produces secondary endocrine effects beyond growth hormone release. Transient elevation of circulating cortisol (via hypothalamic corticotropin-releasing hormone stimulation) and prolactin (via hypothalamic mechanism) are consistently observed following acute GHS-R1a agonist administration [2, 5, 6]. These effects are transient, resolving within 6 to 8 hours of dosing, and are attenuated with repeated administration, suggesting desensitization of the hypothalamic-pituitary-adrenal component of GHS-R1a signaling [17]. Sustained elevation of IGF-1 is observed with chronic dosing, reflecting the downstream hepatic response to sustained pulsatile GH elevation [6].

4.5 Constitutive receptor activity

GHS-R1a exhibits substantial constitutive (agonist-independent) signaling activity, approximately 50 percent of maximal Gq/11 activation in the absence of agonist [18]. This constitutive activity contributes to tonic regulation of appetite and energy homeostasis. Capromorelin, as a full agonist, drives the receptor to maximum signaling capacity above this constitutive baseline. The constitutive activity of GHS-R1a is the molecular basis for the observation that inverse agonists at this receptor can suppress appetite and reduce body weight, while agonists like capromorelin enhance appetite above the already-active baseline. The high constitutive activity has implications for drug development: full agonists produce effects that represent the increment above basal signaling, and the magnitude of pharmacological response depends on both ligand intrinsic efficacy and baseline receptor occupancy.

4.6 Peripheral and gastrointestinal effects

GHS-R1a activation by capromorelin produces additional peripheral effects beyond GH release and appetite stimulation. These include: stimulation of gastric acid secretion and gastrointestinal motility through both central (vagal) and peripheral (enteric nervous system) GHS-R1a activation [14, 19]; modulation of glucose homeostasis through direct pancreatic beta-cell effects and indirect GH-mediated insulin antagonism; and modest effects on the cardiovascular system (heart rate variability, vagal tone) mediated by brainstem GHS-R1a expression [14]. The gastrointestinal prokinetic effects motivated the Phase I study in spinal cord injured volunteers (Ellis et al. 2015) and represent a potential therapeutic application distinct from the GH-releasing and appetite-stimulating indications [5].

4.7 Selectivity

Capromorelin is selective for GHS-R1a over GHS-R1b (the truncated, non-signaling splice variant) and over other G-protein coupled receptors tested in standard selectivity panels. Cross-reactivity with other peptide hormone receptors (motilin receptor, neurotensin receptors, opioid receptors) has not been reported at concentrations up to 10 micromolar [1, 2]. The selectivity profile supports the attribution of in vivo pharmacological effects to GHS-R1a activation.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Capromorelin is rapidly absorbed following oral administration. In dogs at the registered dose of 3 mg/kg, peak plasma concentration (C_{max}) is achieved at approximately 0.83 hours (T_{max}), consistent with rapid gastric emptying and upper intestinal absorption of the lipophilic peptidomimetic [7, 15]. In rats at 3 mg/kg oral dose, absorption occurs within the first hour to an average apparent C_{max} of 1.44 micrograms per milliliter [2]. In human volunteers receiving single ascending oral doses of 20, 50, and 100 mg, dose-proportional increases in C_{max} and AUC were observed, with T_{max} values broadly consistent with the animal pharmacokinetic profile [5].

Food effect data in dogs indicate modest attenuation of C_{max} without significant effect on overall exposure (AUC). The veterinary label recommends administration without regard to food timing.

5.2 Distribution

In radiolabeled distribution studies in rats, CP-424,391 showed wide tissue distribution to peripheral organs including liver, kidney, lung, and gastrointestinal tract, with minimal distribution to the central nervous system [2, 16]. The limited CNS penetration is consistent with the peripheral (pituitary and hypothalamic circumventricular) sites of GHS-R1a-mediated growth hormone release, as the median eminence and anterior pituitary lie outside the blood-brain barrier. Volume of distribution in dogs is approximately 2.0 L/kg, indicating moderate tissue distribution beyond the plasma compartment [15]. Plasma protein binding is moderate; the unbound fraction is approximately 51 percent in dog plasma [15].

5.3 Metabolism

Capromorelin is metabolized predominantly in the liver through cytochrome P450 enzymes. In vitro studies using human liver microsomes and in vivo studies in rats identified CYP3A4 and CYP3A5 as the principal metabolizing enzymes [15, 16]. The

primary metabolic transformations are phase I reactions including N-dealkylation and O-debenzylation, producing pharmacologically inactive metabolites that undergo subsequent phase II glucuronidation [16]. Kamath et al. (2001) characterized the metabolic profile in rats following administration of radiolabeled CP-424,391, identifying multiple hydroxylated and dealkylated metabolites in plasma, bile, urine, and feces [16]. The metabolic profile is consistent across species (rat, dog, human microsomes), supporting the translational pharmacokinetic modeling that informed human dose selection.

The CYP3A4/3A5 dependence implies susceptibility to drug-drug interactions with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir) and inducers (rifampin, carbamazepine, phenytoin, St. John's wort). The veterinary label notes that drugs inhibiting CYP3A4 and CYP3A5 may affect capromorelin metabolism [15].

5.4 Elimination

In dogs, the terminal elimination half-life of capromorelin is approximately 1.19 hours, with a mean total plasma clearance of 18.9 mL/min/kg [15]. In rats, the plasma terminal elimination half-life was 2.4 hours [2]. Excretion is predominantly biliary/fecal (62 percent of administered radioactivity within 72 hours in rats) with a renal component (37 percent) [16]. Less than 10 percent of the administered dose is excreted unchanged in urine. The short half-life is pharmacologically relevant: it permits pulsatile GH stimulation that mimics physiological GH secretion patterns rather than sustained GH elevation, which is associated with adverse metabolic consequences including insulin resistance and fluid retention [4, 14].

In humans, the Phase I study reported dose-dependent plasma exposure with pharmacokinetic parameters broadly similar between able-bodied and spinal cord injured participants, with slightly delayed Tmax and half-life in the spinal cord injured group (attributed to altered gastrointestinal motility) [5].

5.5 Oral bioavailability

The mean absolute oral bioavailability of capromorelin in dogs is 44 percent; in rats, approximately 65 percent [2, 15]. Human oral bioavailability has not been formally reported but the dose-proportional pharmacokinetics and robust pharmaco-

dynamic response (GH elevation) at oral doses of 20 to 100 mg support adequate oral absorption for therapeutic effect.

5.6 Routes of administration

Capromorelin is administered exclusively by the oral route in both veterinary clinical practice and human clinical research. The compound is formulated as an oral solution (30 mg/mL for dogs, 18 mg/mL for cats) for veterinary use and was administered as oral capsules or solution in human clinical trials [6, 7, 8]. Parenteral formulations have been used in preclinical research (intravenous and intraperitoneal in rodent pharmacology studies) but are not developed for clinical application [2].

5.7 Special populations

In the Ellis et al. (2015) Phase I study, spinal cord injured individuals showed greater variance in pharmacokinetic parameters compared to able-bodied controls, with slightly delayed Tmax and modestly prolonged half-life [5]. These differences are consistent with altered gastrointestinal motility and splanchnic blood flow in spinal cord injury and are not considered clinically significant for dose adjustment. No formal renal or hepatic impairment pharmacokinetic studies have been published in humans. The veterinary label advises caution in dogs with hepatic dysfunction (as CYP3A4-mediated metabolism may be impaired) and in animals with renal insufficiency [15].

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Pan et al. (2001) characterized the in vitro pharmacology of CP-424,391 in rat pituitary cell cultures [2]. The compound stimulated GH release with an EC₅₀ of 3 nM, confirming potent functional activity at the pituitary level. Intracellular calcium mobilization was demonstrated using fluorescent calcium indicators, confirming Gq/11-coupled signaling. The compound did not elevate intracellular cAMP, distinguishing its signaling from GHRH receptor activation. At higher concentrations, CP-424,391 modulated the GH-releasing effects of GHRH and the inhibitory effects of somatostatin, demonstrating functional interaction between the GHS-R1a and GHRH/somatostatin receptor systems at the pituitary level [2].

6.2 In vivo growth hormone release in rodents

In anesthetized rats, intravenous CP-424,391 produced dose-dependent pulsatile GH release with onset within 15 minutes and peak effect at 30 to 60 minutes, with an intravenous ED₅₀ of less than 0.05 mg/kg [2]. Oral administration to conscious rats at doses of 1 to 10 mg/kg produced dose-dependent GH elevation detectable in serial plasma sampling. The GH release was pulsatile in character (multiple peaks over 2 to 4 hours), distinguishing the pharmacodynamic response from the sustained GH elevation produced by exogenous GH administration and consistent with the physiological pattern of GH secretion.

6.3 In vivo growth hormone release in dogs

Oral CP-424,391 administration to conscious beagle dogs produced robust, dose-dependent pulsatile GH release [2]. This canine pharmacodynamic demonstration was particularly relevant to the subsequent veterinary development program and confirmed oral bioactivity in a large-animal model with GH physiology more similar to humans than rodents. Serial sampling studies documented distinct GH peaks followed by return to baseline, mimicking the endogenous ultradian GH secretory rhythm [9].

6.4 Chronic dosing studies in dogs

Zollers et al. (2017) reported a 12-month safety study of daily oral capromorelin administration to laboratory dogs at doses of 3 mg/kg (1x clinical dose), 15 mg/kg (5x), and 52.5 mg/kg (17.5x) [17]. At the clinical dose, adverse events were limited to mild emesis and loose stools. At 5x and 17.5x doses, additional findings included hypersalivation and transient cortisol elevation. No clinically significant hematological, clinical chemistry, organ weight, or histopathological findings were identified at any dose level over 12 months. Serum IGF-1 was elevated in a dose-dependent manner throughout the study, confirming sustained GH axis activation. Serum and urinary glucose concentrations were not altered even at 17.5x the clinical dose, indicating absence of diabetogenic effect at the studied exposures in dogs [17].

6.5 Appetite and body weight effects in dogs

Zollers et al. (2016) demonstrated that capromorelin at 3 mg/kg once daily increased food consumption, body weight, GH secretion, and sustained IGF-1 concentrations in healthy adult beagle dogs over a 4-week study period [20, 21]. The appetite-stimulating effect was evident within the first day of dosing and was sustained throughout the treatment period without tachyphylaxis.

6.6 Studies in cats

In laboratory cats, capromorelin at 2 and 6 mg/kg daily for 91 days produced sustained increases in food intake, body weight, GH, and IGF-1 relative to placebo, with adverse effects limited to mild post-dosing salivation and head shaking [9]. Wofford et al. (2020) specifically characterized the effect of capromorelin on glucose metabolism in healthy cats, demonstrating transient postprandial glucose increases that remained within the feline reference range and did not produce persistent hyperglycemia or diabetes at studied doses [22].

6.7 Gastrointestinal motility

Ghrelin receptor agonism produces prokinetic effects on gastrointestinal motility through both central (vagal) and peripheral (enteric nervous system) GHS-R1a activation [14, 19]. Preclinical studies in rodent models have demonstrated that GHS-R1a agonists stimulate gastric emptying, increase colonic motility, and promote

defecation [19]. These effects motivated the Ellis et al. (2015) Phase I study in spinal cord injured volunteers and represent a potential therapeutic application distinct from the GH-releasing and appetite-stimulating indications [5].

6.8 Bone and muscle anabolic effects

Growth hormone secretagogue-mediated elevation of GH and IGF-1 produces anabolic effects on both bone and skeletal muscle in preclinical models [4, 14]. Chronic GHS-R1a agonist administration in aged animals increases bone mineral density, enhances periosteal bone formation, and increases muscle fiber cross-sectional area. These effects are mediated primarily through IGF-1-dependent signaling in osteoblasts and myocytes and are the preclinical basis for the human frailty and sarcopenia indication studied in the White et al. (2009) trial [6].

7. Clinical Evidence Base

7.1 Phase I: Single ascending dose in healthy volunteers and spinal cord injured patients

Ellis et al. (2015) conducted a Phase I single ascending dose safety and pharmacokinetics study of oral capromorelin in 6 able-bodied healthy volunteers and 6 participants with chronic spinal cord injury (SCI), at doses of 20, 50, and 100 mg administered at least one week apart [5]. The rationale for inclusion of SCI participants was the potential therapeutic application of GH axis stimulation for preservation of lean mass and bone mineral density in the setting of neurological immobility, and the prokinetic effects of GHS-R1a agonism for neurogenic bowel dysfunction.

Results demonstrated: (a) safety and tolerability at all dose levels in both populations, with no serious adverse events; (b) dose-proportional increases in C_{max} and AUC; (c) broadly similar pharmacokinetic behavior between able-bodied and SCI groups, with slightly delayed T_{max} and increased variability in the SCI group; (d) GH stimulation at all dose levels as confirmed by post-dose GH sampling; and (e) transient cortisol elevation that normalized within 8 hours [5]. The study supported advancement to further clinical evaluation and confirmed the safety of doses substantially higher than the veterinary therapeutic range.

7.2 Phase II: Efficacy in older adults with functional limitation

White et al. (2009) reported the results of a randomized, double-blind, placebo-controlled, multicenter Phase II study conducted at 13 United States sites, published in the Journal of Clinical Endocrinology and Metabolism [6]. The study enrolled 395 men and women aged 65 to 84 years with mild functional limitation (defined as self-reported difficulty in performing two or more instrumental activities of daily living or moderate physical tasks) and randomized them to one of four capromorelin dosing regimens or placebo:

- Group 1: 10 mg three times per week
- Group 2: 3 mg twice daily

- Group 3: 10 mg every night
- Group 4: 10 mg twice daily
- Group 5: Placebo

The intended treatment duration was 24 months; the study was terminated at 12 months due to a Pfizer strategic portfolio decision.

Primary efficacy results at 12 months:

Lean body mass (measured by dual-energy X-ray absorptiometry): All active treatment groups demonstrated significant increases relative to placebo, with a pooled mean increase of 1.4 kg at 6 months and 1.6 kg at 12 months. The lean mass gain was dose-dependent across the four regimens.

Total body weight: Active treatment groups gained approximately 1.5 kg of total body weight, reflecting the combined anabolic (lean mass) and orexigenic (fat mass) effects of GHS-R1a agonism. The concurrent weight gain partially offset the proportional lean mass benefit.

IGF-1 concentrations: Significant sustained elevation in all active treatment groups relative to placebo, confirming chronic GH axis activation.

Stair climbing power: Significant improvement at 12 months in pooled active treatment groups relative to placebo, representing a functional performance endpoint relevant to the target population [6].

Safety: Capromorelin was generally well tolerated. The principal adverse events were those attributable to the GHS-R1a mechanism: increased appetite, mild weight gain, fatigue, insomnia, and dose-related increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance. No serious adverse events attributable to the study drug were identified. The metabolic safety signal was consistent with Phase I findings and with the broader growth hormone secretagogue class.

Limitations and interpretation: The early termination at 12 months precluded assessment of the 24-month functional endpoints that were the intended primary efficacy measures. The lean mass and IGF-1 findings confirm target engagement and anabolic efficacy but do not constitute evidence of clinically meaningful functional benefit at the level required for registration. The concurrent weight gain (fat

plus lean) is a class effect of GHS-R1a agonists that limits the proportional lean mass benefit and raises the question of net clinical value in elderly populations already at risk for metabolic syndrome [6].

7.3 Veterinary pivotal trials in dogs

Zollers et al. (2016) reported the pivotal field efficacy study of capromorelin oral solution in client-owned dogs with reduced appetite [21]. Dogs (n = 177) were randomized to capromorelin 3 mg/kg or placebo once daily for 4 days. Primary endpoints were owner-assessed appetite score and body weight change. Results demonstrated significantly increased appetite (approximately 7 of 10 owners reported increased appetite versus 4.5 of 10 for placebo) and significant body weight gain in the capromorelin group relative to placebo over the 4-day treatment period. Adverse events were mild and included diarrhea, vomiting, polydipsia, and hypersalivation [21].

7.4 Veterinary pivotal trials in cats

The Elura pivotal study enrolled cats with chronic kidney disease (IRIS stages 2 to 4) and documented unintended weight loss [8]. Capromorelin at 2 mg/kg once daily produced weight gain in more than 80 percent of treated cats over a 56-day study period compared to approximately 40 percent of control cats. The weight gain was sustained throughout the treatment period and was accompanied by improved body condition scoring. The most common adverse reactions in cats were vomiting and hypersalivation, both observed more frequently in male cats [8].

7.5 Anti-doping and sports medicine considerations

Capromorelin has been identified as a substance of interest in anti-doping surveillance due to its GH-releasing activity. Lange et al. (2021) characterized the metabolites of capromorelin (alongside macimorelin and tabimorelin) as potential markers for doping control purposes, identifying specific urinary metabolites suitable for detection by liquid chromatography-tandem mass spectrometry [23]. The compound is prohibited in sport under the World Anti-Doping Agency prohibited list category S2 (Peptide Hormones, Growth Factors, Related Substances, and Mimetics).

8. Sourcing and Quality Verification

Research-grade capromorelin is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich/MilliporeSigma, Cayman Chemical, MedChemExpress, Tocris, Selleckchem, InvivoChem, BocSci, and others) at greater than 98 percent purity by HPLC [24]. Supply is in milligram to gram quantities as the tartrate salt or free base. Pricing is moderate, in the range of \$80 to \$300 per 50 mg depending on supplier and quantity at the time of monograph preparation.

Veterinary pharmaceutical-grade capromorelin (Entyce, 30 mg/mL oral solution; Elura, 18 mg/mL oral solution) is available by veterinary prescription and represents the highest quality, regulatory-validated source with complete quality documentation. These formulations are manufactured under current Good Manufacturing Practice (cGMP) conditions and carry a certificate of analysis with identity, potency, purity, sterility, and stability data [15].

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

- High-performance liquid chromatography area-percent purity (target greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (506.27 [M+H]⁺ for the protonated free base)
- Nuclear magnetic resonance spectroscopy (1H-NMR) confirmation of structural identity
- Chiral HPLC or specific rotation confirmation of diastereomeric purity ((1R,3aR) configuration, greater than 98 percent diastereomeric excess)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent verification of vendor certificates of analysis. The research-grade capromorelin market is well established and material quality is generally reliable from established suppliers; however, on-receipt analytical confirmation is appropriate for any investigation requiring precise dose-response characterization.

9. Reconstitution and Handling

Capromorelin tartrate is soluble in water at room temperature. For research applications, the compound is supplied as a crystalline powder and is reconstituted as needed for in vitro or in vivo studies.

Stock solution preparation: Typical stock concentrations are 10 to 50 mM in dimethyl sulfoxide (DMSO) for in vitro receptor binding and cell-based assays, or 1 to 10 mg/mL in normal saline or phosphate-buffered saline for in vivo administration. Aqueous solubility of the tartrate salt is sufficient for most in vivo dosing volumes. For oral gavage in rodent studies, the compound can be dissolved directly in vehicle (methylcellulose suspension, carboxymethylcellulose, or simple aqueous solution) at concentrations up to 10 mg/mL.

Storage: Solid compound should be stored at minus 20 degrees Celsius or at 2 to 8 degrees Celsius in a desiccated, light-protected container. The tartrate salt is stable at room temperature for short periods (days to weeks) but long-term storage at reduced temperature is recommended to minimize hydrolytic degradation. DMSO stock solutions should be stored at minus 20 degrees Celsius and are stable for at least 6 months; repeated freeze-thaw cycles (up to 5) do not produce measurable potency loss in the structural class.

Aqueous solutions: Freshly prepared aqueous solutions are recommended for in vivo dosing. Solutions in normal saline or buffered vehicles should be used within 24 hours of preparation at room temperature or within 7 days if stored at 2 to 8 degrees Celsius.

Aliquoting: Single-use aliquots are recommended to avoid repeated freeze-thaw cycles. While formal freeze-thaw stability data specific to capromorelin have not been published, the dipeptide mimetic structural class is generally stable to 3 to 5 freeze-thaw cycles in DMSO without measurable potency loss.

Veterinary formulation: The commercial Entyce solution (30 mg/mL capromorelin as the tartrate in a flavored aqueous vehicle with preservatives) is supplied in multi-dose bottles (10 mL, 15 mL, and 30 mL sizes) and is stable at controlled room temperature (20 to 25 degrees Celsius) for the labeled shelf life [15].

Light sensitivity: The compound is not extensively photolabile but routine light protection during storage is reasonable practice for research-grade material.

10. Stack Interactions and Combinations

Investigators conducting research with capromorelin, especially in combination with other research compounds or in the context of chronic dosing regimens, should consider the following interaction categories:

CYP3A4/3A5 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, erythromycin, ritonavir, cobicistat) may substantially increase capromorelin plasma concentrations and prolong its duration of action by reducing hepatic clearance. The veterinary label identifies this interaction [15]. Concurrent use warrants consideration of dose reduction.

CYP3A4/3A5 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) may reduce capromorelin exposure and blunt pharmacodynamic response. Concurrent use may require dose adjustment upward or selection of an alternative GHS-R1a agonist with a different metabolic pathway.

Growth hormone releasing hormone and analogs: Capromorelin synergizes with GHRH to produce GH release greater than either agent alone through convergence of Gq/11 and Gs signaling pathways [2]. The combination of a GHS-R1a agonist with a GHRH analog (sermorelin, tesamorelin, CJC-1295) is pharmacologically rational for maximizing GH pulse amplitude and is used in some research protocols. The combination may increase the metabolic adverse-event signal (glucose, insulin) proportionally.

Somatostatin analogs: Octreotide, lanreotide, and pasireotide suppress GH release through Gi-mediated inhibition of cAMP in somatotrophs. Capromorelin partially overcomes somatostatin suppression through the independent Gq/11-calcium pathway, but concurrent use of somatostatin analogs will attenuate the GH-releasing efficacy of capromorelin [2].

Other GHS-R1a agonists: Concurrent administration with other GHS-R1a agonists (ibutamoren, anamorelin, macimorelin) produces pharmacologically redundant receptor activation. The combination is not recommended and does not produce benefit beyond single-agent administration.

Insulin and insulin secretagogues: The GH-mediated insulin antagonism produced by capromorelin (elevated fasting glucose, insulin resistance) may counteract the effects of insulin, metformin, sulfonylureas, and other glycemic agents. Concurrent use requires monitoring of glycemic parameters.

Glucocorticoids: Exogenous glucocorticoids suppress GH secretion and may attenuate the efficacy of capromorelin. Additionally, the combination of GH-axis activation with glucocorticoid-induced insulin resistance may produce additive metabolic adverse effects.

QT-prolonging agents: GHS-R1a agonists have not been associated with clinically significant QT prolongation, but the cardiovascular effects of GH elevation (cardiac hypertrophy, fluid retention on chronic dosing) warrant monitoring in combination with cardioactive agents.

Appetite suppressants: Concurrent use with GLP-1 receptor agonists (semaglutide, liraglutide, tirzepatide) or melanocortin receptor agonists produces pharmacologically opposing effects on appetite and energy balance. The combination is of research interest for dissecting orexigenic versus anabolic effects of GHS-R1a agonism but is not a rational therapeutic strategy.

Prokinetic agents: The gastrointestinal prokinetic effects of capromorelin may be additive with other prokinetic agents (metoclopramide, erythromycin, prucalopride). The combination is pharmacologically plausible for neurogenic bowel dysfunction but has not been formally studied.

11. Adverse Events and Safety

11.1 Common adverse events in human clinical trials

The principal adverse events observed in the White et al. (2009) Phase II trial at doses of 3 to 20 mg daily for up to 12 months were [6]:

- Increased appetite (pharmacologically expected; mild in magnitude beyond the therapeutic intent)
- Fatigue (modest increase over placebo)
- Insomnia (modest increase over placebo)
- Increased fasting glucose (dose-related, small absolute magnitude)
- Increased glycosylated hemoglobin (dose-related)
- Increased indices of insulin resistance (HOMA-IR elevation)
- Mild weight gain including fat mass component

No serious adverse events attributable to capromorelin were reported. The metabolic signal (glucose, HbA1c, insulin resistance) is consistent with the pharmacology of sustained GH/IGF-1 axis activation and is the principal safety consideration for any future human chronic dosing application [6].

In the Phase I single ascending dose study (20, 50, 100 mg oral), no serious adverse events were reported in either able-bodied or spinal cord injured participants [5]. Transient cortisol elevation was observed at all dose levels, normalizing within 8 hours. Mild gastrointestinal symptoms were reported at the 100 mg dose level but did not limit dosing.

11.2 Common adverse events in dogs (veterinary clinical data)

At the registered dose of 3 mg/kg once daily, the most commonly reported adverse events are [7, 15, 21]:

- Diarrhea (mild, transient; approximately 12 percent)
- Vomiting (mild; approximately 9 percent)

- Elevated blood urea nitrogen (mild, not progressive)
- Polydipsia (increased water intake; approximately 5 percent)
- Hypersalivation (transient, post-dosing; approximately 4 percent)

These adverse events are consistent with the GHS-R1a mechanism and are generally self-limiting.

11.3 Common adverse events in cats (veterinary clinical data)

At the registered dose of 2 mg/kg once daily, the most commonly reported adverse events are [8]:

- Vomiting (more frequent in male cats)
- Hypersalivation (transient, post-dosing; more frequent in males)
- Mild transient hyperglycemia (within reference range)

The cat formulation label advises caution in cats with heart disease or severe dehydration, consistent with the fluid balance and cardiovascular effects of GH axis stimulation [8].

11.4 Long-term safety in dogs

The Zollers et al. (2017) 12-month safety study in laboratory dogs at doses up to 17.5x the clinical dose (52.5 mg/kg daily) identified no clinically significant hematological, clinical chemistry, organ weight, or histopathological findings [17]. Serum and urinary glucose concentrations were not altered even at the highest dose, indicating absence of diabetogenic effect in dogs at the studied exposures. The cortisol stimulation following each dose attenuated progressively over the 12-month period, indicating desensitization of the HPA component. No adrenal hypertrophy or Cushingoid phenotype was observed [17].

11.5 Cortisol stimulation

Transient cortisol elevation is a consistent pharmacodynamic effect of GHS-R1a agonism across species. In dogs, serum cortisol peaks at approximately 2 hours post-dosing and returns to baseline by 6 to 8 hours [17]. The magnitude of cortisol stimu-

lation attenuates with repeated daily dosing. No Cushingoid phenotype or adrenal hypertrophy has been observed in chronic dosing studies.

11.6 Theoretical concerns for chronic human use

The principal theoretical safety concerns for chronic capromorelin administration in humans, extrapolated from the class pharmacology and the White et al. (2009) metabolic signal, include [6]:

- Progressive insulin resistance and glucose intolerance with chronic GH/IGF-1 axis activation
- Theoretical risk of neoplastic promotion through sustained IGF-1 elevation (epidemiological data link elevated IGF-1 to colorectal, breast, and prostate cancer risk, though causality is not established for GHS-mediated IGF-1 elevation)
- Fluid retention (edema, joint stiffness) characteristic of GH-axis activation at higher doses
- Carpal tunnel syndrome with chronic GH elevation (observed with exogenous GH therapy)

The short half-life of capromorelin, producing pulsatile rather than sustained GH elevation, may mitigate some of these risks compared to longer-acting agents or exogenous GH, but this has not been demonstrated in controlled comparisons.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five growth hormone secretagogue candidates against capromorelin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators represent the principal GHS-R1a agonists with substantive clinical or preclinical evidence for growth hormone releasing, appetite-stimulating, or anabolic applications.

12.1 Ibutamoren (MK-677, L-163,191)

Mechanism: Non-peptide spiroindanylpiperidine GHS-R1a full agonist with high binding affinity (K_i approximately 1 to 2 nM). Structurally distinct from capromorelin. Distinguished by its substantially longer half-life (approximately 4 to 6 hours) producing sustained rather than pulsatile GH/IGF-1 elevation [10, 25].

Development trajectory: Merck developed ibutamoren through extensive Phase II clinical trials in growth hormone deficient adults, elderly subjects with hip fracture, obese males, and Alzheimer's disease. The Nass et al. (2008) trial in 65 elderly adults demonstrated significant increases in fat-free mass (1.6 kg) and IGF-1 relative to placebo at 25 mg daily over 12 months [25]. A 2-year trial demonstrated sustained IGF-1 elevation without tachyphylaxis. Despite positive anabolic signals, Merck did not advance ibutamoren to Phase III registration for any human indication. The compound was never approved for clinical use but remains widely available as a research chemical and is sold in the unregulated supplement market [25, 26].

Novelty: Low. The compound has been studied for over 25 years and is the prototypical oral non-peptide GHS-R1a agonist.

Effect size: Moderate. Fat-free mass gains of 1.6 kg at 12 months in elderly adults are comparable to capromorelin Phase II results (1.6 kg lean mass at 12 months). IGF-1 elevation is sustained and robust.

Promising potential: Low for clinical development (no active registration program). Moderate for research applications (widely available, extensively characterized).

Side-effect profile: The long half-life produces sustained GH elevation throughout the dosing interval, which is associated with higher rates of fluid retention, peripheral edema, arthralgias, and insulin resistance compared to shorter-acting GHS-R1a agonists [25, 26]. Appetite stimulation and weight gain (including fat mass) are more pronounced and sustained. The metabolic adverse-event profile is less favorable than capromorelin owing to the sustained (rather than pulsatile) nature of GH stimulation.

Overall validation: Moderate. Extensive Phase II human data over multiple indications, well-characterized pharmacology, but no clinical registration.

Comparison to capromorelin: Ibutamoren has a longer duration of action, more sustained GH/IGF-1 elevation, and more extensive human clinical data. Capromorelin has the advantages of a shorter half-life (preserving physiological GH pulsatility), regulatory validation through veterinary approvals, and a more favorable metabolic safety profile attributable to pulsatile rather than sustained GH stimulation. For research applications requiring pulsatile GH physiology, capromorelin is preferred; for sustained anabolic effect, ibutamoren has stronger data.

12.2 Anamorelin (ONO-7643, RC-1291)

Mechanism: Non-peptide GHS-R1a full agonist with very high binding affinity ($IC_{50} = 0.69$ nM). Developed specifically for cancer anorexia-cachexia syndrome [27, 28].

Development trajectory: Helsinn Healthcare developed anamorelin through Phase III registration trials (ROMANA 1 and ROMANA 2) in patients with non-small cell lung cancer and cachexia. Both Phase III trials met their co-primary endpoint of increased lean body mass (approximately 1.0 to 1.5 kg versus placebo over 12 weeks) but missed the handgrip strength co-primary endpoint [28, 29]. The compound is approved in Japan (2021) for cancer cachexia but has not received FDA or EMA approval due to the failed strength endpoint. The ROMANA 3 extension study confirmed the safety profile over 24 weeks [29].

Novelty: Moderate. The application to cancer cachexia represents a distinct therapeutic positioning within the GHS-R1a agonist class.

Effect size: Moderate for lean mass (1.0 to 1.5 kg over 12 weeks in cachectic patients); absent for functional strength (no improvement in handgrip). The dissociation between lean mass gain and functional improvement is a significant translational limitation.

Promising potential: Moderate to high. Approved in Japan; under review in other jurisdictions.

Side-effect profile: Generally well tolerated in Phase III cancer cachexia trials. Principal adverse events include hyperglycemia (approximately 3 to 5 percent) and peripheral edema [28, 29]. The safety profile in a cachectic cancer population differs from healthy elderly subjects and is difficult to compare directly to capromorelin.

Overall validation: High. Two positive Phase III trials on one co-primary endpoint, regulatory approval in one jurisdiction, and extensive safety database in oncology patients.

Comparison to capromorelin: Anamorelin has more advanced clinical validation (Phase III, approval in Japan) and a specific registered indication (cancer cachexia). Capromorelin has the advantage of veterinary regulatory validation, a shorter half-life producing pulsatile GH release, and a distinct target population (age-related functional decline versus cancer cachexia). The two compounds address different clinical needs within the GHS-R1a agonist class.

12.3 Macimorelin (AEZS-130, EP-01572)

Mechanism: Non-peptide benzolactam-derived GHS-R1a agonist developed as a diagnostic agent rather than a therapeutic. Binding affinity in the low-nanomolar range [30].

Development trajectory: Aeterna Zentaris (subsequently Novo Nordisk) developed macimorelin as an oral diagnostic test for adult growth hormone deficiency (AGHD). The compound was approved by the FDA in December 2017 (marketed as Macrilen) for the diagnosis of AGHD through measurement of GH response to a single oral dose of 0.5 mg/kg [30]. The diagnostic application exploits the consistent, rapid GH stimulation produced by GHS-R1a agonism as a provocation test; it is not intended for chronic therapeutic dosing.

Novelty: High within the diagnostic context. Macimorelin is the only FDA-approved oral GH stimulation test and represents a conceptually distinct application of GHS-R1a agonism (single-dose diagnostic provocation rather than chronic therapeutic anabolism).

Effect size: Not applicable in the therapeutic sense. Diagnostic sensitivity and specificity for AGHD are approximately 87 percent and 96 percent, respectively, versus insulin tolerance test [30].

Promising potential: High for diagnostic application (FDA-approved, marketed). Not developed for chronic therapeutic use.

Side-effect profile: Single-dose administration produces transient taste disturbance (dysgeusia, approximately 10 percent), nausea, dizziness, and headache. These are self-limiting within hours [30].

Overall validation: High for diagnostic application. The compound validates the GHS-R1a agonist mechanism for consistent GH provocation and demonstrates that a single oral dose can produce a standardized GH response suitable for clinical decision-making.

Comparison to capromorelin: Macimorelin occupies a fundamentally different therapeutic niche (diagnostic versus therapeutic). The two compounds share the GHS-R1a agonist mechanism but are not clinical alternatives. Macimorelin's regulatory success validates the target and mechanism; capromorelin's Phase II data validate the chronic anabolic potential.

12.4 Ipamorelin

Mechanism: Pentapeptide GHS-R1a agonist (H-Aib-His-D-2-Nal-D-Phe-Lys-NH₂) with selective GH-releasing activity and minimal effects on cortisol and prolactin at GH-stimulating doses, distinguishing it from earlier less selective peptide GHS (GHRP-6, hexarelin) [31].

Development trajectory: Novo Nordisk developed ipamorelin as a research tool and potential therapeutic. Phase II clinical trials evaluated ipamorelin for postoperative ileus (intravenous administration) based on the prokinetic effects of GHS-R1a agonism. The compound demonstrated selective GH release without significant cortisol or prolactin stimulation in clinical studies [31, 32]. A Phase III trial for post-

operative ileus did not meet its primary endpoint; development was subsequently discontinued. The compound is widely used as a research peptide and in the clinical peptide therapy space (off-label) [31].

Novelty: Moderate. The selectivity for GH release over ACTH/cortisol/prolactin is pharmacologically distinctive within the GHS-R1a agonist class. However, the peptide structure limits oral bioavailability and requires parenteral administration.

Effect size: Moderate for GH release. Modest gastrointestinal prokinetic effect in Phase II postoperative ileus studies; insufficient effect in Phase III.

Promising potential: Low for regulatory development (discontinued). Moderate for research applications (widely available, well-characterized selectivity profile).

Side-effect profile: Favorable. The selectivity for GH over ACTH and cortisol is the principal safety advantage over earlier peptide GHS and over most non-peptide GHS-R1a agonists including capromorelin [31]. Adverse events in Phase II trials were mild (nausea, headache, injection site reactions).

Overall validation: Low to moderate. Phase II positive, Phase III negative for postoperative ileus. No approved indication.

Comparison to capromorelin: Ipamorelin requires parenteral (IV or SC) administration, limiting convenience relative to oral capromorelin. Ipamorelin's selectivity for GH release (minimal cortisol/ACTH effects) is an advantage for applications where cortisol stimulation is undesirable. Capromorelin has the practical advantage of oral bioavailability and the regulatory advantage of FDA-approved veterinary indications. For GH-selective peptide administration in controlled research settings, ipamorelin is preferred; for oral convenience and regulatory-validated supply chain, capromorelin is preferred.

12.5 Tabimorelin (NN703)

Mechanism: Non-peptide GHS-R1a agonist developed by Novo Nordisk. Structurally related to the benzolactam class [33].

Development trajectory: Novo Nordisk advanced tabimorelin through Phase II clinical trials in growth hormone deficient adults. A 4-week randomized double-blind placebo-controlled trial in adult GHD patients demonstrated significant GH and IGF-1 elevation at oral doses of 20 to 80 mg daily [33]. However, the compound

produced unfavorable metabolic effects (hyperglycemia, insulin resistance) at doses producing meaningful IGF-1 elevation, and the therapeutic window between GH stimulation and metabolic toxicity was narrow. Development was discontinued in approximately 2002 due to the unfavorable therapeutic index.

Novelty: Low. The mechanism is conventional GHS-R1a agonism without a distinctive feature.

Effect size: Moderate for GH/IGF-1 elevation; limited by concurrent metabolic toxicity at effective doses.

Promising potential: Low. Development is discontinued. The compound persists as a research tool and a cautionary example of the narrow therapeutic window in GHS-R1a agonist development.

Side-effect profile: Unfavorable. Clinically significant hyperglycemia and insulin resistance at doses required for meaningful GH stimulation. The metabolic safety profile was the principal reason for discontinuation [33].

Overall validation: Low. The compound progressed through Phase II with positive pharmacodynamic endpoints but unacceptable metabolic safety.

Comparison to capromorelin: Capromorelin has a substantially more favorable metabolic safety profile than tabimorelin, attributable to its shorter half-life, pulsatile GH stimulation pattern, and the absence of persistent hyperglycemia in 12-month preclinical and clinical studies. Tabimorelin's failure illustrates the importance of pharmacokinetic optimization (short half-life, pulsatile GH release) in the GHS-R1a agonist class and highlights capromorelin's pharmacokinetic advantage.

12.6 Comparator summary

The five compounds represent the diversity of the GHS-R1a agonist clinical landscape. **Ibutamoren** is the most extensively studied non-peptide oral GHS-R1a agonist with the longest clinical history, moderate anabolic efficacy, but sustained GH elevation that compromises metabolic safety. **Anamorelin** has the most advanced clinical validation (Phase III, Japanese approval) for cancer cachexia but missed functional endpoints and has a restricted indication. **Macimorelin** achieved FDA approval for a diagnostic (not therapeutic) indication, validating the receptor mechanism in a regulatory context. **Ipamorelin** represents the selective peptide GHS subclass with a clean safety profile but parenteral requirement and discontin-

ued development. **Tabimorelin** demonstrated the narrow therapeutic window of GHS-R1a agonists with less favorable pharmacokinetics and was terminated for metabolic toxicity.

Capromorelin occupies a distinctive position in this comparator landscape: it is the only compound with FDA approval in any species for a therapeutic (not diagnostic) indication; its short half-life preserves physiological GH pulsatility and confers a favorable metabolic safety profile relative to longer-acting agonists; its Phase II human data demonstrate anabolic efficacy in the target elderly population; and its oral bioavailability and established manufacturing provide operational accessibility for research applications. The principal limitation relative to the comparators is the absence of Phase III human registration data. The veterinary approvals, while not directly translatable to human registration, validate target engagement, manufacturing, and chronic safety in a relevant large-animal model and provide a practical supply chain for research-grade material.

Investigators considering capromorelin for research applications should expect: robust acute GH stimulation and appetite effects; moderate chronic anabolic efficacy (approximately 1.5 kg lean mass gain over 12 months at studied human doses); transient cortisol and glucose elevation resolving within hours; and a favorable safety profile relative to longer-acting comparators. The compound is well suited to research questions requiring pulsatile GH axis activation, appetite physiology investigation, or comparative pharmacology within the GHS-R1a agonist class.

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