

RESEARCH MONOGRAPH . COMPOUND PROFILE

Anamorelin

A small-molecule peptidomimetic ghrelin receptor agonist developed from the Novo Nordisk growth hormone secretagogue program, approved in Japan for the treatment of cancer cachexia in non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer, and investigated in osteosarcopenia and other wasting conditions.

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ABSTRACT

Anamorelin (ONO-7643, RC-1291, ST-1291) is a non-peptidic, orally active, centrally penetrant agonist of the growth hormone secretagogue receptor type 1a (GHSR-1a), the endogenous receptor for ghrelin. Structurally derived from peptidomimetic optimization of the growth hormone-releasing peptide scaffold at Novo Nordisk and subsequently developed by Helsinn Healthcare and Ono Pharmaceutical, anamorelin binds the ghrelin receptor with subnanomolar affinity (K_i 0.70 nM) and produces full agonist activity in fluorescence imaging plate reader (FLIPR) calcium mobilization assays with an EC_{50} of 0.74 nM, comparable to endogenous ghrelin (K_i 0.58 nM, EC_{50} 0.67 nM) [1]. No antagonist activity has been observed at concentrations up to 1000 nM. The compound is distinguished from endogenous ghrelin by oral bioavailability, a plasma elimination half-life of approximately 7 to 12 hours (compared to approximately 30 minutes for ghrelin), and the absence of peptidic instability. Pharmacodynamically, a single oral dose of 100 mg produces rapid and sustained elevation of circulating growth hormone (GH), insulin-like growth factor 1 (IGF-1), and insulin-like growth factor-binding protein 3 (IGFBP-3), with secondary increases in appetite, caloric intake, and body weight observed on chronic dosing. The principal clinical application is cancer anorexia-cachexia syndrome (CACS). Two pivotal Phase 3 randomized, double-blind, placebo-controlled trials (ROMANA 1 and ROMANA 2), conducted in 979 patients with inoperable stage III or IV non-small cell lung cancer and cachexia across 93 sites in 19 countries, demonstrated that anamorelin 100 mg daily for 12 weeks significantly increased lean body mass (median change +1.10 kg versus -0.44 kg on placebo in ROMANA 1;

+0.75 kg versus -0.96 kg in ROMANA 2; both $P < 0.001$) and body weight, with concurrent improvement in anorexia-cachexia symptoms and quality of life measures [2]. However, both trials failed to demonstrate statistically significant improvement in the co-primary endpoint of handgrip strength, a finding that became the basis for the European Medicines Agency refusal of marketing authorization in 2017 [3]. In Japan, where a separate Phase 2 trial (ONO-7643-04) in Japanese non-small cell lung cancer patients with cachexia and a Phase 3 open-label study (ONO-7643-05) in gastrointestinal cancer cachexia confirmed lean body mass and body weight increases, anamorelin received manufacturing and marketing approval from the Pharmaceuticals and Medical Devices Agency on December 11, 2020, as the first ghrelin receptor agonist approved worldwide for cancer cachexia [4]. It is marketed as Adlumiz tablets (50 mg) by Ono Pharmaceutical and has been available since April 2021 for the treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, or colorectal cancer. Pharmacokinetics are characterized by rapid oral absorption (time to peak concentration 0.5 to 2.0 hours), a pronounced food effect (4-fold reduction in area under the curve when administered with food), hepatic metabolism predominantly through cytochrome P450 3A4 (CYP3A4) with minor contributions from CYP2C8 and CYP2D6, and fecal excretion of approximately 92 percent of the administered dose [5, 6]. The CYP3A4 dependence produces clinically significant drug-drug interaction potential with strong CYP3A4 inhibitors (ketoconazole increases the AUC of anamorelin by approximately 4-fold). The compound depresses cardiac conduction and has sodium channel-blocking activity; prolongation of the PR interval, QRS complex, and QT interval has been observed in clinical trials, with a frequency of approximately

10.7 percent for conduction system abnormalities in Japanese registration studies [7, 8]. Contraindications include congestive heart failure, recent myocardial infarction or angina pectoris, and severe cardiac conduction defects. The most frequent adverse events are hyperglycemia (5 to 6 percent overall, substantially higher in patients with pre-existing diabetes), elevated gamma-glutamyl transpeptidase, and gastrointestinal symptoms. This monograph reviews the chemistry, synthesis, and structural pharmacology of anamorelin; the ghrelin receptor mechanism in molecular and physiological detail; comprehensive pharmacokinetics including food effect and CYP3A4 interaction; the preclinical pharmacology in rat, pig, and tumor xenograft models; the clinical evidence base across the ROMANA program, Japanese registration studies, and the osteosarcopenia indication; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety signals; and a comparative assessment of five cachexia and wasting treatment candidates (ibutamoren, enobosarm, megestrol acetate, mirtazapine, and espindolol) against anamorelin 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: Anamorelin.

Marketed name: Adlumiz (Ono Pharmaceutical; Japan).

Development codes: ONO-7643 (Ono Pharmaceutical), RC-1291 (Helsinn Healthcare / Sapphire Therapeutics), ST-1291 (Sapphire Therapeutics). The development code RC-1291 is the identifier used in the ROMANA Phase 3 clinical trial publications; ONO-7643 is the identifier used in the Japanese registration program [1, 4].

Chemical Abstracts Service registry numbers: 249921-19-5 (free base), 861998-00-7 (hydrochloride salt). The hydrochloride salt is the formulated and marketed form (Adlumiz tablets 50 mg).

International Union of Pure and Applied Chemistry name: 2-amino-N-[(2R)-1-[(3R)-3-benzyl-3-(2,2-dimethylhydrazine-1-carbonyl)piperidin-1-yl]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]-2-methylpropanamide. The compound is a peptidomimetic containing an indole ring system (derived from tryptophan), a piperidine moiety, and a terminal dimethylhydrazide group.

Other identifiers: PubChem CID 9828911; ChemSpider 8004650; UNII DD5RBA1NKF.

1.2 Structural class and chemistry

Anamorelin is a non-peptidic peptidomimetic growth hormone secretagogue derived from systematic truncation and backbone N-methylation of the growth hormone-releasing peptide scaffold. The structural class places it within the small-molecule ghrelin mimetics, a group that includes macimorelin (diagnostic agent for adult growth hormone deficiency), capromorelin (veterinary appetite stimulant), and ipamorelin (peptidic growth hormone secretagogue). The compound was derived from the Novo Nordisk medicinal chemistry program that produced ipamorelin, through sequential reduction of peptide character to achieve oral bioavailability [9].

Molecular formula: C₃₁H₄₂N₆O₃ (free base); C₃₁H₄₃ClN₆O₃ (hydrochloride salt).

Molecular weight: 546.72 g/mol (free base); 583.17 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder. The hydrochloride salt is soluble in water and in common polar organic solvents (methanol, dimethyl sulfoxide). The compound contains two defined stereocenters, both in the R-configuration: one at the alpha-carbon of the tryptophan-derived residue and one at the 3-position of the piperidine ring.

Stereochemistry: Anamorelin is supplied as the single (R,R)-diastereomer. The stereochemical assignment is critical for ghrelin receptor binding; the (S,S)- and mixed diastereomers show substantially reduced receptor affinity. Investigators acquiring research-grade anamorelin should confirm diastereomeric purity by chiral high-performance liquid chromatography.

1.3 Synthesis

The synthesis of anamorelin proceeds through a convergent strategy combining three principal fragments: the 2-methylalanine (alpha-aminoisobutyric acid) capping group, the D-tryptophan central residue, and the 3-benzylpiperidine-3-carboxylic acid trimethylhydrazide fragment [9, 10]. The piperidine fragment is typically prepared by alkylation of a piperidine-3-carboxylate ester with benzyl bromide, followed by hydrazide formation with 1,2,2-trimethylhydrazine. Peptide coupling of the D-tryptophan residue to the piperidine nitrogen is performed using standard amide bond-forming reagents (carbodiimides or uronium reagents such as HATU or HBTU). The 2-methylalanine cap is introduced at the final coupling step. Salt formation with hydrogen chloride in diethyl ether or dioxane produces the hydrochloride salt, which is purified by recrystallization. Crystal form studies have been reported in patent literature [10]. The overall synthesis is moderate in complexity, typically 6 to 8 linear steps, and is amenable to scale-up for pharmaceutical manufacturing.

2. Abstract

Anamorelin (ONO-7643, RC-1291) is a potent, orally active, non-peptidic agonist of the growth hormone secretagogue receptor type 1a (GHSR-1a), the G protein-coupled receptor through which endogenous ghrelin exerts its orexigenic, somatotrophic, and metabolic effects [1, 11]. The compound binds the ghrelin receptor with a K_i of 0.70 nM and produces full agonist activity in fluorescence imaging plate reader (FLIPR) calcium mobilization assays with an EC_{50} of 0.74 nM, comparable to endogenous ghrelin (K_i 0.58 nM, EC_{50} 0.67 nM) [1]. No antagonist activity has been observed at concentrations up to 1000 nM.

The principal pharmacodynamic consequences of GHSR-1a activation are stimulation of growth hormone release from anterior pituitary somatotrophs (with consequent elevation of circulating IGF-1 and IGFBP-3), activation of hypothalamic orexigenic pathways (neuropeptide Y and agouti-related peptide neurons in the arcuate nucleus), and direct peripheral metabolic effects on adipose tissue and skeletal muscle. These activities produce a composite anabolic and appetite-stimulating profile that has been exploited for the treatment of cancer anorexia-cachexia syndrome, a debilitating condition affecting 50 to 80 percent of patients with advanced malignancy and contributing independently to morbidity and mortality [12].

Clinical development has centered on the ROMANA program: two pivotal Phase 3 trials (ROMANA 1, $n = 484$; ROMANA 2, $n = 495$) in patients with stage III/IV non-small cell lung cancer and cachexia, conducted across 93 sites in 19 countries [2]. Anamorelin 100 mg daily for 12 weeks significantly increased lean body mass relative to placebo in both trials ($P < 0.001$) and produced concurrent improvements in body weight, fat mass, and anorexia-cachexia symptom scores. However, neither trial demonstrated significant improvement in the co-primary endpoint of hand-grip strength, a dissociation between body composition and functional endpoints that has shaped the regulatory trajectory of the compound. A safety extension study (ROMANA 3, $n = 513$) confirmed maintenance of body weight and symptom improvements over 12 to 24 weeks of additional treatment [13].

The European Medicines Agency refused marketing authorization in 2017, citing marginal lean body mass effects and absent functional endpoints [3]. The Japanese Pharmaceuticals and Medical Devices Agency approved the compound in

December 2020 on the basis of the ROMANA data, a confirmatory Japanese Phase 2 trial (ONO-7643-04), and a Phase 3 open-label study in gastrointestinal cancer cachexia (ONO-7643-05) [4]. The compound is not approved by the United States Food and Drug Administration and is not included in the 2020 American Society of Clinical Oncology guidelines for cancer cachexia management.

Beyond oncology, a Phase 2 trial of anamorelin 100 mg daily for 12 months in adults with osteosarcopenia (Dawson-Hughes et al. 2024) demonstrated significant increases in knee flexion torque and a 75 percent increase in the bone formation marker serum P1NP, without significant change in lean body mass as measured by the D3-creatine dilution method [14]. This study represents the first evaluation of anamorelin in a non-cancer indication.

3. Discovery and Development History

3.1 Origin

The growth hormone secretagogue receptor was identified through the reverse pharmacology of synthetic hexapeptide growth hormone-releasing peptides (GHRPs), beginning with the Bowers laboratory characterization of GHRP-6 in the 1980s and culminating in the Howard et al. (1996) cloning and characterization of the receptor from porcine pituitary cDNA libraries [15]. The discovery of ghrelin as the endogenous ligand for GHSR-1a by Kojima et al. (1999) established the receptor as a legitimate drug target for appetite and metabolic regulation [16].

Novo Nordisk initiated a medicinal chemistry program to develop orally active, non-peptidic GHSR-1a agonists from the ipamorelin peptide scaffold. The strategy employed sequential backbone N-methylation and non-natural amino acid substitution to reduce peptide character while preserving receptor affinity. Anamorelin emerged from this program as a truncated peptidomimetic retaining the indole pharmacophore (from the tryptophan residue), the piperidine ring (replacing the peptide backbone), and the hydrazide terminus, with oral bioavailability achieved through the reduction of hydrogen bond donors and the introduction of metabolically stable substituents [9].

3.2 Licensing and early development

Novo Nordisk licensed the compound to Sapphire Therapeutics (later acquired by Helsinn Healthcare S.A., Switzerland) for global development. In October 2006, Ono Pharmaceutical entered a license agreement with Sapphire Therapeutics to develop and commercialize anamorelin hydrochloride (designated ONO-7643) in Japan, South Korea, and Taiwan [4]. Helsinn retained rights for the rest of the world and sponsored the ROMANA Phase 3 program.

3.3 Clinical development timeline

Phase 1 studies in healthy volunteers established the pharmacokinetic profile, the food effect, the GH secretory response, and the dose-response relationship for appetite stimulation [17, 18]. Garcia and Polvino (2009) demonstrated dose-dependent increases in plasma GH, IGF-1, and body weight in healthy volunteers receiving anamorelin 25 to 75 mg daily for 6 days [17].

Phase 2 development included a multicenter, randomized, double-blind, placebo-controlled trial (Garcia et al. 2015) in 82 patients with advanced non-small cell lung cancer and cachexia, demonstrating lean body mass increases of 1.89 kg at 100 mg daily over 12 weeks [19]. A separate Japanese Phase 2 trial (ONO-7643-04, Takayama et al. 2016) in NSCLC patients confirmed the lean body mass and body weight findings in a Japanese population [20].

Phase 3 development comprised the ROMANA program (ROMANA 1, ROMANA 2, and ROMANA 3), conducted between 2011 and 2014 [2, 13]. The ROMANA results were published in The Lancet Oncology in 2016.

3.4 Regulatory trajectory

Helsinn submitted a marketing authorization application to the European Medicines Agency in 2016. The Committee for Medicinal Products for Human Use (CHMP) recommended refusal on May 18, 2017, confirmed on September 14, 2017, on the grounds that the lean body mass effect was marginal and that handgrip strength, the co-primary functional endpoint, was not improved, leaving the clinical relevance of the body composition changes uncertain [3].

In Japan, Ono Pharmaceutical filed a manufacturing and marketing approval application in November 2018. The Pharmaceuticals and Medical Devices Agency approved Adlumiz tablets 50 mg on December 11, 2020, for cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, or colorectal cancer, making anamorelin the first ghrelin receptor agonist approved worldwide for cancer cachexia [4]. Commercial launch occurred in April 2021. An 8-year post-marketing re-examination period was mandated.

No application has been filed with the United States Food and Drug Administration.

4. Mechanism of Action

Anamorelin is a selective agonist of the growth hormone secretagogue receptor type 1a (GHSR-1a), a seven-transmembrane G protein-coupled receptor expressed on anterior pituitary somatotrophs, hypothalamic arcuate nucleus neurons, vagal afferent neurons, and multiple peripheral tissues including the gastrointestinal tract, pancreas, heart, and immune cells. The receptor signals primarily through Gq/11 and Gi/o pathways, with downstream activation of phospholipase C, inositol trisphosphate generation, intracellular calcium mobilization, and activation of the mitogen-activated protein kinase cascade [11, 15].

4.1 Growth hormone secretion

GHSR-1a activation on anterior pituitary somatotrophs stimulates pulsatile GH release through a mechanism complementary to, but distinct from, growth hormone-releasing hormone (GHRH) receptor signaling. Anamorelin produces dose-dependent GH release in vitro in rat pituitary cell preparations (EC₅₀ 1.5 nM) and in vivo following oral administration in rats (2.3- to 4.1-fold increase in plasma GH at 3 to 30 mg/kg) and in pigs (acute GH spike following 3.5 mg/kg) [1]. In healthy human volunteers, a single 25 mg oral dose of anamorelin produces rapid and sustained elevation of circulating GH, with peak GH levels at 0.5 to 2 hours post-dose [17, 18]. The GH elevation is followed by secondary increases in IGF-1 and IGFBP-3 with chronic dosing, consistent with hepatic IGF-1 synthesis in response to sustained GH signaling. In pig studies, repeated daily dosing at 1 mg/kg produced significant IGF-1 elevation (21 percent above control) but attenuated GH response by day 7, consistent with negative feedback regulation of the GH axis [1].

4.2 Orexigenic activity

GHSR-1a is expressed at high density on neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus, the principal central regulators of appetite and energy homeostasis. Ghrelin receptor activation on these neurons stimulates NPY and AgRP release, which in turn inhibits the anorexigenic pro-opiomelanocortin (POMC) neurons and drives appetite and food-seeking behavior. Anamorelin activates this pathway following oral administration,

producing measurable increases in subjective appetite and caloric intake in Phase 1 studies [17, 18]. In rat studies, 6-day oral administration at 3, 10, and 30 mg/kg produced significant dose-dependent increases in food intake and body weight at all dose levels, with effects apparent by day 2 of treatment [1].

4.3 Anabolic and metabolic effects

The composite downstream effects of GH and IGF-1 elevation include stimulation of skeletal muscle protein synthesis, positive nitrogen balance, lipolysis in adipose tissue, and hepatic glucose output. In cancer cachexia, where catabolic cytokine signaling (tumor necrosis factor alpha, interleukin-6, myostatin) drives progressive loss of lean tissue, anamorelin-mediated GH/IGF-1 axis activation provides a countervailing anabolic signal. The clinical demonstration of lean body mass increases in the ROMANA trials is consistent with this anabolic mechanism, though the absence of handgrip strength improvement suggests that the body composition effect may include fluid redistribution or non-contractile tissue rather than purely functional muscle accrual [2].

4.4 Cardiac conduction effects

Anamorelin has sodium channel-blocking activity that is independent of the ghrelin receptor mechanism. This activity produces dose-dependent depression of cardiac conduction, manifest as prolongation of the PR interval, widening of the QRS complex, and prolongation of the QT interval [7, 8]. The mechanism involves direct blockade of voltage-gated sodium channels (Nav1.5) in cardiac myocytes, analogous to the Class I antiarrhythmic mechanism. This off-target activity is the basis for the cardiac contraindications and for the monitoring requirements in the Japanese prescribing information.

4.5 Selectivity

Anamorelin demonstrates high selectivity for GHSR-1a over other G protein-coupled receptors. In broad-panel receptor screening, weak binding was observed at NK2 (neurokinin-2) receptors and at serotonin receptors, but these interactions occur at concentrations substantially above those achieved at clinical doses and are not considered pharmacologically relevant except in massive overdose [1]. Structural studies have revealed that anamorelin and macimorelin occupy a bifur-

cated binding pocket in the GHSR-1a transmembrane domain, divided by a conserved salt bridge between E124(3.33) and R283(6.55), with the indole pharmacophore of anamorelin engaging the aromatic cage at the receptor core [21].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Anamorelin is rapidly absorbed after oral administration in the fasted state, with time to peak plasma concentration (T_{max}) of 0.5 to 2.0 hours in healthy volunteers [17, 18, 5]. The compound demonstrates a pronounced food effect: administration with food decreases the area under the concentration-time curve (AUC) by approximately 4-fold compared to the fasted state [5]. This interaction is clinically significant and is the basis for the prescribing instruction to administer anamorelin on an empty stomach, at least one hour before the first meal of the day.

5.2 Distribution

The volume of distribution has not been published in detail in the clinical pharmacology literature. The compound is centrally penetrant, as demonstrated by its hypothalamic orexigenic activity and by the GH secretory response mediated through pituitary GHSR-1a. Protein binding data have not been published in peer-reviewed form.

5.3 Metabolism

Anamorelin is metabolized predominantly in the liver by cytochrome P450 3A4 (CYP3A4), with minor contributions from CYP2C8 and CYP2D6 [5, 6]. In vitro studies with human hepatic microsomes and recombinant CYP isoforms have identified multiple metabolites arising from oxygenation (hydroxylation of the indole ring and the piperidine ring) and N-demethylation of the terminal hydrazide group [6]. A comprehensive metabolite identification study by Rzeppa et al. (2023) using human hepatocytes and liquid chromatography-high resolution mass spectrometry identified 18 metabolites through oxygenation, N-demethylation, desaturation, and combination pathways [6]. The metabolites are pharmacologically inactive or substantially less active than the parent compound at GHSR-1a.

The CYP3A4 dependence produces clinically significant drug-drug interaction potential. Co-administration with ketoconazole (a strong CYP3A4 inhibitor) increases the AUC of anamorelin by approximately 4-fold [5]. This interaction necessitates dose adjustment or avoidance of concurrent strong CYP3A4 inhibitors.

5.4 Elimination

The plasma elimination half-life of anamorelin is approximately 7 to 12 hours, substantially longer than the approximately 30-minute half-life of endogenous ghrelin and consistent with once-daily oral dosing [1, 5]. Elimination is predominantly fecal: mass balance studies with radiolabeled anamorelin demonstrate that approximately 92 percent of the administered dose is recovered in feces, with the remainder in urine [5]. The fecal elimination reflects both biliary excretion of hepatic metabolites and unabsorbed parent compound.

5.5 Routes of administration

The only clinically developed route is oral administration. The registered dose in Japan is 100 mg once daily (two 50 mg Adlumiz tablets), administered on an empty stomach at least one hour before the first meal. The prescribing information specifies discontinuation if no effect is observed after 3 weeks of treatment, and notes that clinical experience beyond 12 weeks is limited [4].

5.6 Special populations

An open-label Phase 1 study (Leese et al. 2015) evaluated the effects of age and gender on anamorelin pharmacokinetics and pharmacodynamics in healthy volunteers aged 19 to 79 years [18]. No clinically significant effects of age or gender on the pharmacokinetic parameters were identified, though sample sizes were small. Formal studies in renal impairment and hepatic impairment have not been published. Given the predominantly hepatic (CYP3A4-mediated) metabolism, hepatic impairment is expected to increase exposure. Pediatric pharmacokinetics have not been characterized. Body weight and body composition (particularly obesity) may affect the volume of distribution and the relationship between dose and plasma concentration, as evidenced by case reports of QT prolongation in obese patients [7].

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Pietra et al. (2014) characterized anamorelin in fluorescence imaging plate reader (FLIPR) calcium mobilization assays in HEK293 cells stably expressing human GHSR-1a, producing full agonist responses with an EC₅₀ of 0.74 nM (95% CI 0.50 to 1.12 nM), comparable to ghrelin (EC₅₀ 0.67 nM) [1]. In radioligand displacement assays using [¹²⁵I]-ibutamoren, the K_i was 0.70 nM (95% CI 0.55 to 0.96 nM), again comparable to ghrelin (K_i 0.58 nM). No antagonist activity was observed at concentrations up to 1000 nM. In rat pituitary cell preparations, anamorelin stimulated dose-dependent GH release with an EC₅₀ of 1.5 nM [1].

Selectivity screening against a panel of 73 receptors, ion channels, and enzymes identified weak binding at NK2 receptors and minor calcium and serotonin interactions, none of which were considered pharmacologically relevant at therapeutic concentrations [1].

6.2 In vivo pharmacology in rats

Six-day oral administration of anamorelin at 3, 10, and 30 mg/kg in rats produced significant dose-dependent increases in food intake and body weight at all dose levels, with effects apparent by day 2 [1]. Single-dose GH secretion studies showed maximum 2.3- to 4.1-fold increases in plasma GH above vehicle control, with peak concentrations at 0.5 to 2 hours post-dose. Mean plasma GH concentration ranged from 10.0 to 143.0 ng/mL in the 3 mg/kg dose group, 11.3 to 197.6 ng/mL in the 10 mg/kg group, and 38.7 to 251.3 ng/mL in the 30 mg/kg group. The GH area under the curve over 6 hours was significantly elevated at the 10 and 30 mg/kg doses ($P < 0.05$) [1].

6.3 In vivo pharmacology in pigs

In miniature pigs, a single oral dose of 3.5 mg/kg produced acute GH release [1]. Repeated daily dosing at 1 mg/kg for 7 days produced significant IGF-1 elevation (21 percent above control) but attenuated GH responses by day 7, consistent with so-

matotroph desensitization or negative feedback through elevated IGF-1. The pig model confirmed cross-species translation of the GHSR-1a agonist pharmacology and the IGF-1 elevation that is central to the anabolic mechanism.

6.4 Tumor growth assessment

A critical safety question for ghrelin receptor agonism in oncology is whether GH and IGF-1 elevation promotes tumor growth. In a mouse non-small cell lung cancer xenograft model (A549 adenocarcinoma), anamorelin at 10 and 30 mg/kg daily produced significant body weight increases without promotion of tumor growth, despite measurable elevation of mouse GH and IGF-1 [1]. Concurrent administration of exogenous ghrelin at doses producing approximately 50-fold GH increases similarly showed no tumor stimulation, even in cells with high IGF-1 receptor expression. These preclinical data support the safety of ghrelin receptor agonism with respect to tumor progression, a finding consistent with the absence of overall survival detriment in the ROMANA clinical trials [2].

6.5 Bone and musculoskeletal effects

The GH-IGF-1 axis is a principal regulator of bone formation and remodeling. GH and IGF-1 stimulate osteoblast differentiation, proliferation, and matrix synthesis through the IGF-1 receptor [22]. Preclinical evidence supporting anabolic bone effects of GHSR-1a agonism provided the rationale for the subsequent clinical investigation of anamorelin in osteosarcopenia [14].

7. Clinical Evidence Base

7.1 Phase 1 studies

Garcia and Polvino (2009) conducted Phase 1 studies in healthy volunteers receiving anamorelin at doses of 25 to 75 mg [17]. All doses produced rapid, dose-dependent growth hormone elevation (peak at 1 to 2 hours), with concurrent increases in IGF-1 and IGFBP-3. Appetite stimulation was assessed by visual analog scale and demonstrated significant increases at all studied doses. No clinically significant effects on prolactin, cortisol, insulin, glucose, ACTH, LH, FSH, or TSH were observed, confirming selectivity for the GH axis. The compound was well tolerated with no dose-limiting adverse events.

Leese et al. (2015) conducted an open-label Phase 1 study examining the effects of age and gender on anamorelin pharmacokinetics and pharmacodynamics in healthy volunteers aged 19 to 79 years [18]. A single 25 mg dose increased circulating GH levels in all cohorts, with no clinically significant age or gender effects on pharmacokinetic parameters.

Leese et al. (2019) reported Phase 1 data demonstrating significant appetite stimulation and food intake increases following single and multiple doses of anamorelin in healthy volunteers, with food intake increases of approximately 16 to 33 percent in a standardized meal paradigm [23].

7.2 Phase 2 studies

Garcia et al. (2015) conducted a Phase 2 randomized, double-blind, placebo-controlled trial in 82 patients with advanced cancer and cachexia, randomized to anamorelin 50 mg, 100 mg, or placebo daily for 12 weeks [19]. The 100 mg dose produced a median lean body mass increase of 1.89 kg (by dual-energy X-ray absorptiometry) and significant improvements in body weight and appetite scores. The 50 mg dose produced intermediate effects. No significant differences in handgrip strength or six-minute walk test were observed. The study established 100 mg as the dose for Phase 3 development.

Takayama et al. (2016) reported a randomized Phase 2 trial (ONO-7643-04) in Japanese patients with NSCLC and cachexia, confirming lean body mass increases of 1.56 kg by DXA and significant body weight increases with anamorelin 100 mg daily [20]. Handgrip strength and six-minute walk test did not differ between groups, consistent with the global Phase 2 findings.

7.3 Phase 3 ROMANA program

ROMANA 1 and ROMANA 2

Temel et al. (2016) reported the pivotal ROMANA 1 and ROMANA 2 trials in *The Lancet Oncology* [2]. Both were randomized, double-blind, placebo-controlled Phase 3 trials conducted at 93 sites in 19 countries. Patients had inoperable stage III or IV NSCLC with cachexia (defined as 5 percent or greater involuntary weight loss within 6 months or body mass index less than 20 kg/m²). Patients were randomized 2:1 to anamorelin 100 mg daily or placebo for 12 weeks. Co-primary endpoints were median change in lean body mass (by DXA) and handgrip strength.

ROMANA 1 enrolled 484 patients (323 anamorelin, 161 placebo). Lean body mass change was +1.10 kg with anamorelin versus -0.44 kg with placebo ($P < 0.001$). ROMANA 2 enrolled 495 patients (330 anamorelin, 165 placebo). Lean body mass change was +0.75 kg versus -0.96 kg ($P < 0.001$). In both trials, body weight, total body mass, and fat mass increased significantly with anamorelin. Anorexia-cachexia symptom scores (FAACT-ACS) improved significantly [2].

However, handgrip strength did not differ significantly between groups in either trial, and the co-primary endpoint was therefore not met. This dissociation between body composition and function has been attributed to several factors: the advanced stage of the underlying malignancy, the relatively short treatment duration, the possibility that lean mass gains included non-contractile tissue or fluid, and the insensitivity of handgrip strength as a measure of whole-body functional capacity in cachectic cancer patients [2].

The most frequent drug-related adverse event was hyperglycemia (5.3 percent in ROMANA 1 and 4.2 percent in ROMANA 2). Overall treatment-related adverse event rates were similar between anamorelin and placebo groups.

ROMANA 3

Currow et al. (2017) reported the Phase 3 safety extension study (ROMANA 3) [13]. Of 703 patients completing ROMANA 1 and 2, 513 entered ROMANA 3 (345 anamorelin, 168 placebo). Body weight increases and anorexia-cachexia symptom improvements observed in the parent trials were maintained over 12 to 24 weeks of additional treatment. Anamorelin significantly increased body weight from baseline of the original trials at all time points ($P < 0.0001$) and improved anorexia-cachexia symptoms at weeks 3, 6, 9, 12, and 16 ($P < 0.05$). Safety was consistent with the parent trials.

Post-hoc analyses

Laird et al. (2025) published a post-hoc analysis of ROMANA 1 and ROMANA 2 examining efficacy by baseline cachexia severity and other subgroup factors [24]. The analysis identified subgroups with greater functional benefit, suggesting that earlier intervention in the cachexia trajectory may improve functional outcomes and that the overall trial populations may have included patients at too advanced a disease stage for functional recovery.

7.4 Japanese registration studies

The ONO-7643-05 study was a Phase 3 multicenter, open-label, uncontrolled study in patients with cachexia associated with advanced, unresectable gastric, pancreatic, or colorectal cancer [4]. Lean body mass improvements (1.89 plus or minus 0.36 kg by DXA) and body weight increases were observed, consistent with the NSCLC data. The study provided the basis for the expanded indication beyond NSCLC in the Japanese approval.

A recent multicenter, open-label, randomized controlled trial (Naito et al. 2025) evaluated anamorelin in patients with unresectable or recurrent gastric cancer and cachexia, further confirming efficacy in gastrointestinal cancer indications [25].

7.5 Osteosarcopenia

Dawson-Hughes et al. (2024) reported a 12-month Phase 2 double-blind, placebo-controlled trial of anamorelin 100 mg daily in 26 men and postmenopausal women with osteosarcopenia [14]. The trial did not demonstrate a significant increase in muscle mass as measured by D3-creatine dilution, a gold-standard measurement.

However, anamorelin significantly increased knee flexion torque at 240 degrees per second by 20 percent ($P = 0.013$) and produced a 75 percent increase in the bone formation marker serum P1NP without significant change in the resorption marker serum CTX, indicating a net anabolic bone remodeling effect. This study represents the first evaluation of anamorelin in a non-cancer indication.

A companion analysis (Dawson-Hughes et al. 2024) examined effects on serum irisin and inflammatory markers, demonstrating anti-inflammatory effects of anamorelin in the non-cancer population [26].

7.6 Regulatory status summary

The compound is approved in Japan (December 2020, Ono Pharmaceutical, Adlumiz tablets 50 mg) for cachexia in NSCLC, gastric, pancreatic, and colorectal cancer [4]. Marketing authorization was refused by the EMA in 2017 [3]. The compound is not approved by the FDA. It is not included in the 2020 ASCO guidelines for cancer cachexia management.

8. Sourcing and Quality Verification

Pharmaceutical-grade anamorelin (Adlumiz brand, Ono Pharmaceutical) is the highest quality source and is available only in Japan. The pharmaceutical material is supplied as 50 mg tablets of the hydrochloride salt. Obtaining pharmaceutical-grade material outside Japan requires importation under research or compassionate use frameworks.

Research-grade anamorelin hydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Cayman Chemical, MedKoo Biosciences, Tocris, Sigma-Aldrich, and others) at purity greater than 98 percent by HPLC. Supply is in milligram to gram quantities as the hydrochloride salt.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (547.34 for the protonated free base $[M+H]^+$)
- Chiral HPLC confirmation of diastereomeric purity (the compound contains two stereocenters and incorrect stereochemistry produces substantially reduced receptor affinity)
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography (common synthesis solvents: dichloromethane, methanol, ethyl acetate, dimethylformamide)

Anamorelin is listed on the World Anti-Doping Agency (WADA) Prohibited List under the category of growth hormone secretagogues (class S2.3), and research-grade material obtained for sports-adjacent or performance research must comply with applicable anti-doping regulations [6].

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The research-grade anamorelin market is established, though lot-to-lot variability in diastereomeric purity has been reported; on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Anamorelin hydrochloride is a crystalline solid soluble in water at room temperature. For research applications, the compound is supplied as a powder and is reconstituted as needed.

In vitro applications: Stock solutions at 10 to 50 mM are typically prepared in dimethyl sulfoxide (DMSO), with working dilutions in assay buffer. At 10 mM, the concentration of the hydrochloride salt is approximately 5.83 mg/mL. DMSO stocks should be aliquoted for single-use to avoid freeze-thaw degradation.

In vivo applications: For oral gavage in rodent studies, the compound can be dissolved directly in water or in 0.5 percent methylcellulose at concentrations of 1 to 10 mg/mL. Higher concentrations may require co-solvents (polyethylene glycol 400, propylene glycol).

Storage of solid: Store at -20 degrees Celsius under desiccation, protected from light. Under these conditions, stability of at least 2 years is expected based on vendor specifications.

Storage of solutions: DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months in sealed, single-use aliquots. Aqueous solutions should be prepared fresh or stored at 2 to 8 degrees Celsius for no more than 7 days.

Clinical formulation: The marketed Adlumiz tablet (50 mg anamorelin hydrochloride) is a film-coated tablet designed for oral administration. Two tablets (100 mg total) constitute the approved daily dose, taken on an empty stomach at least one hour before the first meal.

Handling precautions: Standard laboratory precautions apply. The compound is not classified as hazardous at research-use quantities, but general caution regarding pharmacologically active growth hormone secretagogues is appropriate. Gloves and eye protection should be worn during handling of the solid and concentrated solutions.

10. Stack Interactions and Combinations

Anamorelin interacts with several drug classes through its CYP3A4-mediated metabolism and through its pharmacodynamic effects on the GH-IGF-1 axis, glucose homeostasis, and cardiac conduction. Investigators conducting research with anamorelin, especially in chronic dosing regimens or in combination with other agents, should consider:

CYP3A4 inhibitors: Strong inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat) increase anamorelin exposure by approximately 4-fold and should be avoided or require dose reduction [5]. Moderate inhibitors (fluconazole, erythromycin, diltiazem, verapamil, grapefruit juice) produce smaller but measurable increases in exposure.

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) are expected to substantially reduce anamorelin exposure, potentially compromising efficacy. This interaction is clinically relevant in cancer patients receiving dexamethasone (a moderate CYP3A4 inducer) as part of chemotherapy antiemetic regimens.

Hypoglycemic agents: Anamorelin elevates blood glucose through GH-mediated insulin resistance and direct ghrelin receptor effects on pancreatic islet cells. In patients with pre-existing diabetes, the incidence of hyperglycemic adverse events is substantially elevated (72.2 percent versus 6.3 percent in non-diabetic patients), and treatment discontinuation due to hyperglycemia is more frequent (25.8 percent versus 4.2 percent) [27]. Concurrent use with insulin or oral hypoglycemic agents requires close glucose monitoring and dose adjustment of the antidiabetic therapy.

QT-prolonging agents: Given the sodium channel-blocking activity and cardiac conduction effects of anamorelin, concurrent use with other QT-prolonging agents (class IA and III antiarrhythmics, fluoroquinolones, macrolides, methadone, ondansetron, haloperidol) increases the risk of clinically significant arrhythmia and should be avoided or approached with ECG monitoring [7, 8].

Other growth hormone secretagogues: Concurrent use with other GHSR-1a agonists (ipamorelin, ibutamoren, macimorelin, capromorelin) or with growth hormone-releasing hormone analogs (tesamorelin, sermorelin) would produce additive or synergistic GH elevation and is pharmacologically redundant. The combination has not been studied clinically.

Corticosteroids: Corticosteroids (dexamethasone, prednisone) are commonly co-administered in cancer patients for appetite stimulation and symptom management. The combination with anamorelin is pharmacologically plausible but may exacerbate hyperglycemia. No formal interaction studies have been conducted, though concurrent use was permitted in the ROMANA program without specific safety signals.

Somatostatin analogs: Octreotide, lanreotide, and pasireotide suppress growth hormone release and oppose the somatotropic actions of anamorelin. Concurrent use produces pharmacodynamic antagonism at the pituitary level.

Chemotherapy agents: In the ROMANA program, anamorelin was administered concurrently with standard chemotherapy regimens for NSCLC without identified pharmacokinetic interactions [2]. No dose adjustment for chemotherapy is required.

Proton pump inhibitors: Gastric pH elevation could theoretically affect anamorelin dissolution and absorption; formal interaction studies have not been published. The clinical trials permitted concurrent proton pump inhibitor use without dose adjustment.

11. Adverse Events and Safety Signal

11.1 Common adverse events

The principal adverse events at the registered 100 mg daily dose, derived from the ROMANA program and the Japanese registration studies, are [2, 4, 13]:

- Hyperglycemia (5.3 percent in ROMANA 1, 4.2 percent in ROMANA 2; 6.1 percent in Japanese studies). Reflects GH counter-regulatory effects on glucose metabolism and ghrelin-mediated suppression of insulin secretion.
- Elevated gamma-glutamyl transpeptidase (8.2 percent in Japanese studies; generally clinically insignificant and reversible on discontinuation)
- Diabetes mellitus exacerbation (6.1 percent in Japanese studies)
- Cardiac conduction effects: PR interval prolongation and QRS widening (6.1 percent in Japanese studies, approximately 10.7 percent for any conduction abnormality). These effects are dose-dependent and reflect sodium channel blocking activity.
- Nausea (3 to 5 percent)
- Peripheral edema (2 to 4 percent; consistent with GH-mediated fluid retention)
- Diarrhea (2 to 3 percent)

11.2 Cardiac adverse events

Cardiac conduction abnormalities are the most clinically significant safety concern. The sodium channel-blocking activity produces dose-dependent depression of the cardiac conduction system. In clinical trials in Japan, patients experienced conduction system depression at a frequency of approximately 10.7 percent [7]. Case reports have documented QT interval prolongation to greater than 500 ms in individual patients, with associated risk of torsade de pointes [7]. Two cases of wide QRS complex tachycardia attributed to anamorelin have been reported in the Japanese post-marketing literature [8].

The risk of clinically significant conduction effects is increased in obese patients (higher volume of distribution, potentially higher tissue concentrations), patients with pre-existing conduction abnormalities, patients receiving concurrent CYP3A4

inhibitors (elevated plasma concentrations), and patients with electrolyte abnormalities (hypokalemia, hypomagnesemia) [7, 8].

11.3 Hyperglycemia in diabetic patients

Patients with pre-existing diabetes represent a high-risk population. Katakami et al. (2024) reported that diabetic patients had a cumulative incidence of hyperglycemic adverse events of 72.2 percent (versus 6.3 percent in non-diabetic patients) and a treatment discontinuation rate due to hyperglycemia of 25.8 percent (versus 4.2 percent) [27]. Anamorelin-induced acute hyperglycemia requiring emergency intervention has been reported in a patient with advanced pancreatic cancer and diabetes [28]. Close glucose monitoring is essential in this population.

11.4 Contraindications

The Japanese prescribing information contraindications are: congestive heart failure; recent myocardial infarction or unstable angina pectoris; and severe cardiac conduction defects (second- or third-degree atrioventricular block, bundle branch block with QRS greater than 120 milliseconds) [4].

11.5 Tumor growth safety

Preclinical studies in NSCLC xenograft models showed no tumor growth promotion with anamorelin despite GH and IGF-1 elevation [1]. In the ROMANA program, no statistically significant effect on overall survival was observed with anamorelin versus placebo, providing clinical reassurance that GH axis stimulation does not accelerate tumor progression in this population [2]. The 8-year post-marketing surveillance period mandated by the Japanese regulatory authority will provide long-term data on this question.

11.6 Pregnancy and lactation

No human pregnancy data are available. Animal reproductive toxicity studies have not been published in the peer-reviewed literature. Given the mechanism (GH/IGF-1 axis stimulation), use during pregnancy and lactation is not recommended.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five cachexia and wasting treatment candidates against anamorelin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation.

12.1 Ibutamoren (MK-677)

Mechanism: Non-peptide growth hormone secretagogue; selective GHSR-1a agonist with full agonist activity. Structurally a benzolactam spiropiperidine, mechanistically identical target to anamorelin.

Development trajectory: Developed by Merck Research Laboratories in the 1990s for growth hormone deficiency and age-related sarcopenia. Phase 2 studies in elderly subjects demonstrated sustained IGF-1 elevation and lean body mass increases over 12 months (Nass et al. 2008) [29]. Phase 2 studies in hip fracture recovery demonstrated improved functional endpoints. The compound was not advanced to Phase 3 registration for any indication.

Novelty: Low. The mechanism is identical to anamorelin (GHSR-1a agonism); the compound predates anamorelin in development but has not achieved registration.

Effect size: Moderate. Lean body mass increases of 1 to 2 kg over 12 months in elderly subjects; IGF-1 elevation sustained over chronic dosing [29]. Effect sizes are similar to anamorelin in the non-cachectic elderly population.

Promising potential: Low. No active commercial development. Not registered in any jurisdiction for any indication.

Side-effect profile: Hyperglycemia, insulin resistance, fluid retention, arthralgia, carpal tunnel symptoms with chronic dosing. No sodium channel blocking activity has been characterized; cardiac safety profile is more favorable than anamorelin.

However, long-term metabolic effects (sustained insulin resistance) may be more prominent given the substantially longer half-life (approximately 24 hours versus 7 to 12 hours for anamorelin).

Overall validation: Moderate. Extensive Phase 2 clinical data; no Phase 3 data; no registration.

Comparison to anamorelin: Ibutamoren and anamorelin share the same molecular target and produce similar pharmacodynamic profiles. Anamorelin has the advantage of Phase 3 clinical evidence in cancer cachexia and regulatory approval in Japan. Ibutamoren has the advantage of the longer half-life (potentially simpler chronic dosing pharmacology) and the absence of characterized sodium channel blocking activity. The two compounds are mechanistically redundant and should not be combined.

12.2 Enobosarm (GTx-024, Ostarine)

Mechanism: Non-steroidal selective androgen receptor modulator (SARM). Produces anabolic effects on muscle and bone through selective activation of androgen receptors in these tissues with reduced androgenic activity in reproductive tissues.

Development trajectory: GTx Inc. (later Oncternal Therapeutics) advanced enobosarm through Phase 2 development for cancer cachexia. Dobs et al. (2013) reported dose-dependent increases in lean body mass in cancer patients (1.0 to 1.5 kg over 16 weeks) [30]. Two Phase 3 trials (POWER 1 and POWER 2) in NSCLC cachexia produced inconsistent results: one trial met the responder analysis endpoint for lean body mass and stair-climbing power, the other did not. The FDA issued a Complete Response Letter. Development for cachexia has been discontinued.

Novelty: Moderate. The SARM mechanism is distinct from ghrelin agonism and addresses the anabolic deficit through a different pathway.

Effect size: Similar to anamorelin. Lean body mass increases of 1 to 1.5 kg over 12 to 16 weeks. Like anamorelin, the lean body mass effect did not consistently translate to functional improvement [30].

Promising potential: Low for cachexia (development discontinued). Moderate for breast cancer (repositioned indication).

Side-effect profile: Generally well tolerated. Hepatic enzyme elevation was the principal safety signal. No cardiac conduction effects. No hyperglycemia.

Overall validation: Low to moderate. Phase 3 inconsistency and regulatory rejection parallel the anamorelin EMA experience.

Comparison to anamorelin: Both compounds produce similar lean body mass increases and both failed to demonstrate consistent functional improvement. Anamorelin has the advantage of regulatory approval (Japan) and concurrent appetite stimulation. Enobosarm has the theoretical advantage of direct muscle anabolic activity independent of GH/IGF-1 elevation.

12.3 Megestrol acetate

Mechanism: Synthetic progestational agent with appetite-stimulating activity through incompletely characterized central mechanisms, possibly involving neuropeptide Y modulation and glucocorticoid-like effects.

Development trajectory: Megestrol acetate (Megace) is the most widely used pharmacological appetite stimulant in cancer cachexia and HIV/AIDS wasting. It is approved by the FDA for appetite stimulation in AIDS-related wasting and is used off-label for cancer cachexia [31].

Novelty: Low. The compound has been available since the 1960s.

Effect size: Body weight increases of 2 to 5 kg over 8 to 12 weeks, predominantly reflecting fat mass and fluid retention rather than lean body mass [31]. No consistent improvement in functional endpoints, quality of life, or survival.

Promising potential: Low. No ongoing development for improved formulations or expanded indications.

Side-effect profile: Thromboembolic events (deep vein thrombosis, pulmonary embolism), adrenal suppression, hyperglycemia, peripheral edema. The thromboembolic risk is the principal safety limitation. Overall safety profile is substantially worse than anamorelin.

Overall validation: Moderate. Extensively studied over three decades with consistent appetite and weight effects but without lean body mass or survival benefit and with a concerning safety profile.

Comparison to anamorelin: Megestrol acetate produces greater absolute weight gain than anamorelin but predominantly through fat and fluid rather than lean mass. Anamorelin has a superior lean body mass effect and a more favorable safety profile (lower thromboembolic risk, lower adrenal suppression risk). Megestrol has the advantage of wider regulatory approval and lower cost.

12.4 Mirtazapine

Mechanism: Noradrenergic and specific serotonergic antidepressant (NaSSA). Appetite-stimulating effects are mediated through histamine H1 receptor antagonism, 5-HT_{2C} receptor antagonism, and 5-HT₃ receptor antagonism.

Development trajectory: Mirtazapine (Remeron) is registered worldwide as an antidepressant and is used off-label for appetite stimulation in cancer patients [32]. Randomized controlled trials in cancer cachexia are limited; a Phase 2 trial (Riechelmann et al. 2010) in cancer patients did not demonstrate significant weight gain [32].

Novelty: Low. The appetite-stimulating application is an off-label use of a well-characterized antidepressant.

Effect size: Modest and inconsistent in cancer cachexia. Weight gain of 1 to 3 kg over 4 to 8 weeks, predominantly fat mass. No lean body mass data.

Promising potential: Low for cachexia as a primary indication. Moderate as adjunctive therapy for patients with concurrent depression and anorexia.

Side-effect profile: Sedation (prominent, dose-dependent), weight gain, dry mouth, constipation. No cardiac conduction effects. No hyperglycemia at the magnitude seen with anamorelin.

Overall validation: Low for cachexia. High as an antidepressant. The cachexia literature is small and negative.

Comparison to anamorelin: Mirtazapine does not activate the GH-IGF-1 anabolic axis and does not produce lean body mass increases. Anamorelin is mechanistically superior for cachexia. Mirtazapine may be appropriate as adjunctive therapy for patients with concurrent depression.

12.5 Espindolol (MT-102)

Mechanism: Non-selective beta-1/beta-2 adrenergic receptor antagonist with partial beta-2 agonism, 5-HT1a agonism, and additional anti-catabolic activity. Designed as a multi-target agent addressing the combined metabolic derangements of cachexia: beta-blockade reduces resting energy expenditure, 5-HT1a agonism provides appetite stimulation, and partial beta-2 agonism produces modest anabolic effects [33].

Development trajectory: PsiOxus Therapeutics (later Actimed Therapeutics) advanced espindolol through the ACT-ONE Phase 2 trial in 87 patients with stage III/IV colorectal or NSCLC and cachexia [33]. The study demonstrated significant increases in lean body mass (0.54 kg versus -0.21 kg on placebo at 16 weeks), significant reductions in resting energy expenditure, and improved handgrip strength at the highest dose tested (10 mg twice daily). The compound has not advanced to Phase 3; further development is uncertain.

Novelty: High. The multi-mechanism beta-blocker approach to cachexia is mechanistically novel and addresses energy expenditure (a component of cachexia not addressed by anamorelin).

Effect size: Moderate. Lean body mass increases of 0.5 to 0.75 kg over 16 weeks, smaller in magnitude than anamorelin. However, the demonstrated improvement in handgrip strength is a qualitative advantage that distinguishes espindolol from anamorelin.

Promising potential: Moderate. Phase 2 complete with positive functional endpoints. Phase 3 development status uncertain.

Side-effect profile: Predictable beta-blocker effects: bradycardia, hypotension, fatigue, bronchospasm risk. These effects may be poorly tolerated in debilitated cancer patients.

Overall validation: Low to moderate. Single Phase 2 trial with encouraging results; no replication; no Phase 3; no registration.

Comparison to anamorelin: Espindolol and anamorelin address cachexia through complementary, non-overlapping mechanisms. Espindolol's demonstrated handgrip strength improvement addresses the principal regulatory weakness of anamorelin. Anamorelin has the advantage of Phase 3 evidence, regulatory ap-

proval, and larger clinical experience. The combination could theoretically produce additive benefits (increased anabolism plus reduced catabolism) but has not been studied.

12.6 Comparator summary

The five compounds occupy distinct positions in the cachexia pharmacotherapy landscape. **Ibutamoren** represents the closest mechanistic comparator (identical target) without Phase 3 evidence or registration. **Enobosarm** addresses lean body mass through androgen receptor activation with Phase 3 evidence paralleling the anamorelin experience (lean mass increase without consistent functional improvement); cachexia development is terminated. **Megestrol acetate** is the clinical standard for appetite stimulation but produces fat mass rather than lean mass gain and carries thromboembolic risk. **Mirtazapine** provides modest off-label appetite benefit without anabolic effects. **Espindolol** is mechanistically novel and is the only comparator that has demonstrated functional improvement (handgrip strength) in addition to lean body mass increase, though with smaller magnitude of lean body mass effect and without Phase 3 confirmation.

Anamorelin occupies a unique position as the only approved pharmacotherapy specifically for cancer cachexia, with the largest Phase 3 evidence base in the class and the most comprehensive characterization of lean body mass effects. Its principal limitation is the dissociation between lean body mass increase and functional improvement (handgrip strength), a limitation shared with enobosarm and one that contributed to the EMA refusal. The Japanese approval establishes regulatory precedent for lean body mass as a meaningful endpoint in cachexia, a decision that may influence future regulatory pathways for cachexia therapeutics in other jurisdictions. The cardiac conduction effects (sodium channel blockade) represent a safety consideration not shared by most comparators and require appropriate monitoring in clinical use.

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