

RESEARCH MONOGRAPH . COMPOUND PROFILE

HGH

A recombinant human growth hormone (somatropin) identical to endogenous pituitary-derived 22-kDa somatotropin, administered by subcutaneous injection for replacement therapy in pediatric and adult growth hormone deficiency, and investigated for body composition optimization, bone density, anti-aging physiology, and recovery from catabolic states.

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ABSTRACT

Human growth hormone (HGH), designated pharmacologically as somatropin in its recombinant form, is a 191-amino-acid, single-chain, non-glycosylated polypeptide of approximately 22,124 daltons produced by recombinant DNA technology in *Escherichia coli* or mammalian cell expression systems. The compound is structurally and functionally identical to the predominant 22-kDa isoform of endogenous somatotropin secreted by somatotrophic cells of the anterior pituitary gland. Recombinant somatropin binds to the extracellular domain of the transmembrane growth hormone receptor (GHR), inducing receptor dimerization and activation of the Janus kinase 2 (JAK2) signaling cascade, with downstream phosphorylation of signal transducers and activators of transcription (STAT1, STAT3, STAT5), mitogen-activated protein kinase (MAPK/ERK), and phosphatidylinositol 3-kinase (PI3K/Akt) pathways. The principal systemic mediator of somatropin action is insulin-like growth factor 1 (IGF-1), a 70-amino-acid peptide synthesized predominantly in hepatocytes under direct GH receptor stimulation and released into the circulation bound to IGF-binding proteins (IGFBPs), principally IGFBP-3 in a ternary complex with the acid-labile subunit (ALS). The GH/IGF-1 axis governs linear bone growth in children, anabolic protein metabolism, lipolysis, glucose counter-regulation, and tissue repair across the lifespan.

The clinical development of exogenous growth hormone spans seven decades. Maurice Raben administered cadaveric pituitary-derived human growth hormone to a growth-hormone-deficient child in 1958, establishing proof of concept for replacement

therapy. Cadaveric extraction remained the sole source until 1985, when reports of iatrogenic Creutzfeldt-Jakob disease (CJD) in recipients of pituitary-derived hormone prompted immediate suspension of cadaveric programs worldwide. Genentech received United States Food and Drug Administration (FDA) approval in October 1985 for somatrem (methionyl-HGH, Protropin), the first recombinant growth hormone product, followed by approval of somatropin (Humatrope, Eli Lilly) in 1987. As of 2026, multiple recombinant somatropin formulations are FDA-approved for pediatric growth hormone deficiency (GHD), Turner syndrome, Prader-Willi syndrome, small for gestational age (SGA) with failure of catch-up growth, idiopathic short stature (ISS), SHOX deficiency, chronic renal insufficiency, and Noonan syndrome in children, and for adult GHD and HIV-associated wasting. Long-acting formulations (somapacitan, somatrogon, lonapegsomatropin) have been approved since 2020 to reduce injection burden from daily to weekly administration.

Pharmacokinetics of subcutaneous somatropin are characterized by slow absorption from the injection depot (time to peak plasma concentration 3 to 5 hours), absolute bioavailability of approximately 70 to 80 percent, volume of distribution of approximately 0.07 L/kg (intravenous) to 1.3 L/kg (subcutaneous, apparent), and elimination half-life of approximately 3 to 4 hours following subcutaneous administration compared to 0.36 hours following intravenous injection. Clearance occurs principally through hepatic and renal proteolytic catabolism. The pharmacodynamic effect, mediated through sustained elevation of circulating IGF-1, persists substantially longer than the plasma half-life of the parent molecule, with IGF-1 levels remaining elevated for 18 to 28 hours after a single subcutaneous dose.

Clinical evidence for somatropin in pediatric GHD is extensive and unequivocal: meta-analyses of controlled trials demonstrate mean adult height gains of 4 to 8 centimeters above predicted untreated height over treatment courses of 3 to 10 years. In adults with documented GHD, randomized placebo-controlled trials demonstrate reduction of trunk fat mass (8 to 16 percent), increase in lean body mass (2 to 5 kg), improvement in bone mineral density at lumbar spine and femoral neck, improvement in lipid profiles (reduction in LDL cholesterol, increase in HDL cholesterol), and improvement in quality-of-life measures. The principal adverse events of somatropin therapy are dose-dependent and related to fluid retention: peripheral edema, arthralgia, myalgia, carpal tunnel syndrome, and paresthesia, occurring more frequently in adults than in children and generally resolving with dose reduction. Insulin resistance with impaired glucose tolerance is a recognized metabolic consequence of supraphysiologic GH exposure and requires monitoring. Long-term surveillance data from registries including KIGS, HypoCCS, NordiNet IOS, and the French SAGhE cohort have not demonstrated a consistent increase in de novo malignancy risk in patients treated for GHD without pre-existing risk factors, although the SAGhE study reported a modestly elevated standardized mortality ratio in patients treated with higher doses during childhood.

This monograph reviews the molecular biology, structural chemistry, and signal transduction pharmacology of recombinant somatropin; the comprehensive pharmacokinetic record; the clinical evidence base across pediatric and adult GHD, body composition, bone metabolism, and investigational applications; sourcing, reconstitution, and handling considerations for research use; stack interactions with secretagogues, IGF-1, insulin, and

thyroid hormones; the adverse event and long-term safety profile; and a structured comparative assessment of five alternative approaches to GH axis modulation (sermorelin, tesamorelin, CJC-1295, ipamorelin, and ibutamoren/MK-677) against recombinant somatropin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Somatropin.

Common abbreviations: HGH (human growth hormone), rhGH (recombinant human growth hormone), GH (growth hormone).

Marketed names: Genotropin (Pfizer), Norditropin (Novo Nordisk), Humatrope (Eli Lilly), Nutropin AQ (Ipsen), Omnitrope (Sandoz), Saizen (Merck Serono), Zomacton (Ferring), Serostim (EMD Serono, HIV-associated wasting indication), Zorbtive (EMD Serono, short bowel syndrome indication), Tev-Tropin (Teva). Historical product: Protropin (Genentech; somatrem, methionyl-HGH, discontinued 2004).

Long-acting formulations: Sogroya (somapacitan, Novo Nordisk; weekly), Ngenla (somatrogon, Pfizer; weekly), Skytrofa (lonapegsomatropin, Ascendis Pharma; weekly).

Chemical Abstracts Service registry number: 12629-01-5 (somatotropin, human). Recombinant somatropin is assigned the same CAS number as the endogenous hormone for the 191-amino-acid form.

European Pharmacopoeia designation: Somatropin for injection, recombinant DNA origin.

United States Pharmacopeia designation: Somatropin.

Drug Enforcement Administration scheduling: Somatropin is listed as a controlled substance under the Anabolic Steroids Control Act amendment of 1990, though it is not itself an anabolic steroid. Distribution or possession without a valid prescription is a federal offense in the United States.

1.2 Structural class and chemistry

Somatropin is a recombinant protein hormone belonging to the somatotropin/prolactin structural superfamily. The molecule is a single-chain, non-glycosylated polypeptide of 191 amino acid residues with a molecular weight of approximately 22,124 daltons. The primary sequence is identical to the predominant 22-kDa isoform encoded by the GH1 gene located on the long arm of chromosome 17 (17q22-24), within a cluster that also contains the GH2 gene and three placental lactogen genes (CSH1, CSH2, CSHL1) [1].

Molecular formula: C990H1528N262O300S7 (approximate, based on the 191-amino-acid sequence).

Disulfide bonds: Two intramolecular disulfide bridges are present: one between Cys-53 and Cys-165, forming a large internal loop of 112 residues, and one between Cys-182 and Cys-189, forming a small loop near the C-terminus. Both disulfide bonds are essential for native tertiary structure and biological activity [2].

Three-dimensional structure: The tertiary structure consists of a four-helix bundle (helices A, B, C, and D) connected by loop regions, characteristic of the class 1 cytokine superfamily. The four-helix bundle presents the two binding sites (site 1 and site 2) required for sequential engagement and dimerization of two GH receptor molecules on the target cell surface. Site 1 (high-affinity) involves residues from helices A and D and the connecting loop; site 2 (lower-affinity) involves residues from helices A and C [3].

Physical properties: White to off-white lyophilized powder in pharmaceutical preparations. Freely soluble in water upon reconstitution. The reconstituted solution has a pH of approximately 6.0 to 8.0 depending on the formulation buffer (phosphate, histidine, or citrate based). Sensitive to mechanical agitation, which can induce aggregation; should not be vigorously shaken.

Isoforms: The GH1 gene produces multiple mRNA splice variants. The predominant isoform is the 22-kDa, 191-amino-acid form that constitutes approximately 85 to 90 percent of circulating pituitary GH. A 20-kDa variant lacking residues 32 to 46 (produced by alternative splicing) constitutes approximately 10 to 15 percent of pituitary secretion and has similar growth-promoting but reduced diabetogenic activity. Recombinant somatropin products contain only the 22-kDa isoform [4].

1.3 Manufacture

Recombinant somatropin is produced by expression of the human GH1 gene in prokaryotic (*Escherichia coli*) or eukaryotic (murine C127 mammary cell line, for the original Genentech Protropin; *Saccharomyces cerevisiae* for some biosimilars) host systems. The *E. coli* expression system, used for the majority of currently marketed products, produces the protein as inclusion bodies, which are solubilized, refolded to native conformation with correct disulfide bond formation, and purified through multiple chromatographic steps (ion exchange, size exclusion, reversed-phase or hydrophobic interaction chromatography). The final product is characterized by high-performance liquid chromatography (HPLC), mass spectrometry, isoelectric focusing, peptide mapping, circular dichroism spectroscopy for secondary structure confirmation, and bioassay (Nb2 lymphoma cell proliferation assay or equivalent) [5]. Pharmaceutical-grade somatropin products meet United States Pharmacopeia or European Pharmacopoeia specifications for identity, purity (greater than 95 percent by reversed-phase HPLC), potency (not less than 3.0 International Units per milligram), bacterial endotoxin content, and host cell protein content.

The historical precursor, somatrem (methionyl-HGH, Protropin), contained an additional N-terminal methionine residue resulting from the *E. coli* expression system. Somatrem was immunogenic at a higher rate than somatropin and was discontinued in 2004 after the development of signal-peptide-based expression systems and improved refolding processes that produced the authentic 191-amino-acid sequence without the extraneous methionine.

2. Abstract

Human growth hormone (somatropin) is the recombinant form of the endogenous 22-kDa anterior pituitary somatotropin, a single-chain 191-amino-acid polypeptide hormone that serves as the principal endocrine regulator of postnatal linear growth, body composition, and intermediary metabolism. The compound acts through binding to the transmembrane growth hormone receptor (GHR), inducing receptor dimerization and activation of the JAK2/STAT5 signaling cascade, with the principal systemic effector being hepatic production and release of insulin-like growth factor 1 (IGF-1) [6, 7].

The therapeutic development of exogenous growth hormone represents one of the longest continuous arcs in endocrine pharmacology. Cadaveric pituitary-derived HGH was administered to GH-deficient children from 1958 through 1985. The discovery of iatrogenic Creutzfeldt-Jakob disease in cadaveric GH recipients precipitated the transition to recombinant production, with the first recombinant product (somatrem) approved in 1985 and authentic-sequence somatropin approved in 1987 [8, 9]. As of 2026, eight daily-injection somatropin products and three weekly long-acting GH formulations are approved in the United States, and the compound is registered in essentially all major pharmaceutical jurisdictions worldwide.

Clinical applications span pediatric and adult endocrinology. In children with documented GHD, treatment with daily subcutaneous somatropin at doses of 0.024 to 0.043 mg/kg/day produces mean adult height gains of 4 to 8 centimeters above predicted untreated height, with optimal outcomes when treatment begins early and continues through epiphyseal fusion [10, 11]. Additional approved pediatric indications include Turner syndrome, Prader-Willi syndrome, small for gestational age, idiopathic short stature, SHOX deficiency, chronic renal insufficiency, and Noonan syndrome. In adults with documented GHD, replacement therapy at doses of 0.1 to 0.8 mg/day produces favorable changes in body composition (reduced trunk fat mass, increased lean body mass), improved bone mineral density, normalization of lipid profiles, and improvement in quality-of-life scores on validated instruments [12, 13].

The pharmacokinetic profile following subcutaneous injection is characterized by slow depot absorption (Tmax 3 to 5 hours), bioavailability of approximately 70 to 80 percent, elimination half-life of 3 to 4 hours, and predominantly hepatic and renal proteolytic clearance. The pharmacodynamic effect through IGF-1 elevation substantially outlasts the parent molecule half-life [14].

The adverse event profile is well characterized across more than 40 years of post-marketing surveillance. Dose-dependent fluid retention effects (edema, arthralgia, carpal tunnel syndrome) are the most common treatment-emergent events and are generally manageable with dose titration. Insulin resistance and impaired glucose tolerance represent the principal metabolic concern, particularly at supraphysiologic doses. Long-term safety surveillance has not identified a consistent signal for increased de novo malignancy in patients without pre-existing risk factors, though the question of risk at high doses over prolonged periods remains under active epidemiological investigation [15, 16].

This monograph documents the structural biology and manufacture of recombinant somatropin; the GH receptor signal transduction pharmacology; comprehensive pharmacokinetics; the clinical evidence base across all approved and investigational indications; sourcing, reconstitution, and handling; stack interactions with GH secretagogues, IGF-1, insulin, and thyroid hormones; the adverse event profile; and a comparative assessment of five alternative GH-axis modulators against recombinant somatropin.

3. Discovery and Development History

3.1 Identification and isolation of growth hormone

The existence of a pituitary growth-promoting factor was established through the classic hypophysectomy and pituitary extract experiments of the early twentieth century. Herbert Evans and Joseph Long at the University of California, Berkeley, demonstrated in 1921 that anterior pituitary extracts produced gigantism in rats. Choh Hao Li, also at Berkeley, achieved the first isolation and purification of growth hormone from bovine pituitary glands in 1944 and from human pituitary glands in 1956. Independently, Maurice Raben at Tufts University Medical Center isolated human growth hormone from cadaveric pituitary tissue in 1956 using an acetone-extraction method [8].

3.2 First clinical use

In 1958, Maurice Raben reported the first successful treatment of a growth-hormone-deficient child with pituitary-derived human growth hormone. The patient, a young boy with hypopituitary dwarfism, grew two inches over ten months of treatment. This demonstration established proof of concept for GH replacement therapy and initiated the cadaveric pituitary era of growth hormone treatment [8].

3.3 The cadaveric pituitary era (1958 to 1985)

Between 1963 and 1985, the National Hormone and Pituitary Program (formerly the National Pituitary Agency) in the United States coordinated the collection of cadaveric pituitary glands and the extraction and distribution of human growth hormone. Approximately 7,700 children in the United States and 27,000 children worldwide received cadaveric pituitary-derived growth hormone during this period. The supply was chronically limited by the availability of cadaveric pituitary tissue, restricting treatment to children with severe GHD and producing substantial unmet demand [9].

3.4 The Creutzfeldt-Jakob disease crisis

In April 1985, the FDA received reports of Creutzfeldt-Jakob disease (CJD) in four young adults in the United States who had received cadaveric pituitary-derived growth hormone during the 1960s and 1970s. CJD is a fatal transmissible spongiform encephalopathy caused by prion contamination. Distribution of pituitary-derived GH was immediately suspended on April 19, 1985. Subsequent epidemiological tracking identified additional cases; by 2012, at least 226 cases of iatrogenic CJD attributable to cadaveric GH had been documented worldwide, with the highest incidence in France (119 cases) and the United Kingdom (65 cases) [17].

3.5 Recombinant era

Genentech had begun development of recombinant human growth hormone in the late 1970s using the then-new recombinant DNA technology. The first recombinant product, somatrem (methionyl-HGH, marketed as Protropin), received FDA approval on October 18, 1985, within months of the suspension of cadaveric GH distribution. Somatrem contained a non-native N-terminal methionine residue and was associated with a higher rate of anti-GH antibody formation than native-sequence GH. In 1987, Eli Lilly received FDA approval for somatropin (Humatrope), produced by a mammalian cell expression system that yielded the authentic 191-amino-acid human sequence without the methionine artifact [9, 18].

3.6 Expansion of approved indications

The initial FDA approval of recombinant GH was limited to pediatric GHD. Subsequent approvals expanded the indications substantially: Turner syndrome (1996), chronic renal insufficiency prior to transplantation (1993), Prader-Willi syndrome (2000), small for gestational age with failure of catch-up growth (2001), idiopathic short stature (2003), SHOX deficiency (2006), Noonan syndrome (2007), and adult growth hormone deficiency (1996 for Humatrope, subsequently for other brands). The HIV-associated wasting indication (Serostim, 1996) and short bowel syndrome indication (Zorbtive, 2003) addressed catabolic and malabsorptive states [19].

3.7 Long-acting formulations

The burden of daily subcutaneous injection has driven development of long-acting GH formulations since the 2000s. Three weekly-administration products have received regulatory approval: somapacitan (Sogroya, Novo Nordisk; FDA-approved for adult GHD in 2020 and pediatric GHD in 2023), somatrogen (Ngenla, Pfizer; FDA-approved for pediatric GHD in 2023), and lonapegsomatropin (Skytrofa, Ascendis Pharma; FDA-approved for pediatric GHD in 2021). These products employ albumin-binding (somapacitan), fusion protein (somatrogen), or prodrug transient conjugation (lonapegsomatropin) strategies to extend the pharmacokinetic half-life from hours to days [20].

4. Mechanism of Action

4.1 Growth hormone receptor binding and dimerization

Somatropin exerts its biological effects through binding to the growth hormone receptor (GHR), a type I transmembrane glycoprotein of the cytokine receptor superfamily expressed at high density on hepatocytes and at lower density on adipocytes, myocytes, chondrocytes, osteoblasts, lymphocytes, and cells of most other tissues. The GHR is a single-pass transmembrane protein with an extracellular domain, a transmembrane helix, and an intracellular domain that lacks intrinsic kinase activity but is constitutively associated with Janus kinase 2 (JAK2) [6].

Growth hormone binding proceeds through a sequential, two-step mechanism. The first binding event occurs at site 1 of the GH molecule (a high-affinity interface involving residues from helices A and D and the A-B loop) to one GHR molecule. The resulting 1:1 GH-GHR complex then engages a second GHR molecule through site 2 of the GH molecule (a lower-affinity interface involving residues from helices A and C), forming the active 1:2 GH-(GHR)₂ ternary complex. This sequential dimerization model was established by the Wells laboratory at Genentech through mutagenesis, surface plasmon resonance, and the landmark de Vos crystal structure of the GH-GHR complex published in 1992 [3, 21]. Receptor dimerization is the obligate activation step; monomeric GH-GHR complexes are signaling-incompetent.

4.2 JAK-STAT signaling cascade

Receptor dimerization brings the intracellular domains of the two GHR molecules into proximity, activating the pre-associated JAK2 tyrosine kinases by trans-phosphorylation. Activated JAK2 phosphorylates tyrosine residues on the intracellular domain of the GHR itself, creating docking sites for SH2-domain-containing signaling molecules. The principal downstream pathways are [7, 22]:

STAT5b pathway: Signal transducer and activator of transcription 5b (STAT5b) is recruited to phosphotyrosine residues on the GHR intracellular domain, is phosphorylated by JAK2, dimerizes, and translocates to the nucleus where it activates transcription of IGF-1, IGFBP-3, the acid-labile subunit (ALS), and multiple other

GH-responsive genes. STAT5b is the principal mediator of the growth-promoting and body-composition effects of GH; loss-of-function mutations in STAT5b produce a phenotype of severe postnatal growth failure with low IGF-1 levels despite normal or elevated GH concentrations.

STAT1 and STAT3 pathways: These transcription factors are activated in parallel and mediate some of the metabolic and immunomodulatory effects of GH.

MAPK/ERK pathway: GH activates the Ras-Raf-MEK-ERK mitogen-activated protein kinase cascade through adaptor proteins (SHC, GRB2, SOS) recruited to the phosphorylated GHR. The MAPK pathway contributes to the proliferative and differentiation signals of GH action in chondrocytes and other cell types.

PI3K/Akt pathway: Phosphatidylinositol 3-kinase is activated through insulin receptor substrate (IRS) proteins recruited to the GHR complex. The PI3K/Akt pathway mediates the acute metabolic effects of GH, including the anti-apoptotic, glucose-transport, and lipogenic responses. This pathway is also the mechanistic basis for the insulin-antagonizing (diabetogenic) effect of GH, as GH-induced PI3K activation in hepatocytes can impair insulin-dependent GLUT4 translocation and glycogen synthesis through competitive substrate-level signaling [23].

4.3 The GH/IGF-1 axis

The dominant systemic mediator of GH action is insulin-like growth factor 1 (IGF-1), a 70-amino-acid, 7,649-dalton peptide synthesized predominantly in hepatocytes in response to GH receptor activation through the STAT5b pathway. Circulating IGF-1 is bound in a ternary complex with IGFBP-3 (or IGFBP-5) and the acid-labile subunit, which extends the circulating half-life of IGF-1 from approximately 10 minutes (free) to 12 to 16 hours (ternary complex) [24].

IGF-1 acts through the type 1 IGF receptor (IGF-1R), a heterotetrameric tyrosine kinase receptor structurally homologous to the insulin receptor. IGF-1R activation triggers the PI3K/Akt and MAPK/ERK pathways in target tissues, producing the growth-promoting, anabolic, and anti-apoptotic effects that constitute the "indirect" actions of growth hormone. The relative contributions of direct GH action (through the GHR) and indirect GH action (through circulating IGF-1) vary by tissue: linear bone growth is predominantly IGF-1-mediated (local and circulating), lipolysis is predominantly a direct GH effect, and muscle protein synthesis is a composite of direct and IGF-1-mediated action [25].

4.4 Direct metabolic effects

Growth hormone exerts multiple direct metabolic effects independent of IGF-1:

Lipolysis: GH stimulates hormone-sensitive lipase activity in adipocytes, increasing free fatty acid mobilization and oxidation. This effect is mediated through JAK2 and downstream activation of protein kinase C and MAPK pathways. The lipolytic effect is the principal mechanism by which GH therapy reduces trunk and visceral fat mass [26].

Gluconeogenesis and insulin antagonism: GH stimulates hepatic gluconeogenesis and opposes insulin action on glucose uptake in peripheral tissues. The diabetogenic effect is dose-dependent and is the basis for the impaired glucose tolerance observed at supraphysiologic GH levels [23].

Protein synthesis: GH stimulates amino acid uptake and protein synthesis in skeletal muscle through both direct (GHR-mediated) and indirect (IGF-1-mediated) mechanisms.

Sodium and water retention: GH activates the renin-angiotensin-aldosterone system and directly stimulates renal tubular sodium reabsorption, producing the fluid retention that underlies the edema, arthralgia, and carpal tunnel syndrome observed during GH therapy [27].

4.5 Negative feedback regulation

Endogenous GH secretion is regulated by the hypothalamic-pituitary feedback loop. Growth hormone-releasing hormone (GHRH) from the arcuate nucleus of the hypothalamus stimulates GH synthesis and secretion; somatostatin (SRIF) from the periventricular nucleus inhibits it. Ghrelin, produced predominantly by gastric oxyntic cells, acts through the growth hormone secretagogue receptor (GHS-R1a) as an additional stimulatory signal. Circulating IGF-1 provides negative feedback at both the hypothalamus (stimulating somatostatin release) and the pituitary (suppressing GH gene transcription and secretion). Exogenous somatotropin administration suppresses endogenous GH secretion through this IGF-1-mediated feedback; the magnitude and duration of suppression are dose-dependent and are the pharmacological basis for the pulsatile dosing rationale and for the concern that chronic supraphysiologic dosing may produce sustained suppression of endogenous secretory capacity [28].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Somatropin is administered by subcutaneous injection (the standard clinical route) or, less commonly, by intramuscular injection. Oral administration is not feasible due to proteolytic degradation in the gastrointestinal tract and negligible oral bioavailability. Following subcutaneous injection, absorption is slow and sustained, forming a depot at the injection site. Time to maximum plasma concentration (T_{max}) is approximately 3 to 5 hours. Absolute bioavailability following subcutaneous administration is approximately 70 to 80 percent; following intramuscular administration, approximately 63 percent [14, 29].

Maximum plasma concentration (C_{max}) after a subcutaneous dose of 0.1 IU/kg (approximately 0.033 mg/kg) in GHD adults is approximately 13 to 35 ng/mL, varying with injection site, subcutaneous tissue thickness, and individual absorption kinetics. Injection site (abdomen, thigh, buttock, upper arm) modestly affects absorption rate but not overall bioavailability; the abdomen generally provides the most rapid absorption.

5.2 Distribution

Volume of distribution following intravenous administration is approximately 0.07 L/kg, consistent with distribution predominantly within the vascular and extracellular fluid compartments. The apparent volume of distribution following subcutaneous administration is larger (approximately 1.3 L/kg in GHD adults), reflecting the absorption-limited pharmacokinetic profile. Somatropin binds to a circulating GH-binding protein (GHBP), which is the proteolytically cleaved extracellular domain of the GH receptor. Approximately 40 to 50 percent of circulating GH is bound to GHBP under physiologic conditions; the binding prolongs the plasma half-life modestly and may serve as a circulating reservoir [30].

5.3 Metabolism

Somatropin is metabolized by classical protein catabolism, principally in the liver and kidneys. Hepatic catabolism involves receptor-mediated endocytosis of the GH-GHR complex followed by lysosomal degradation to constituent amino acids. Renal catabolism involves glomerular filtration of the free (non-GHBP-bound) fraction followed by tubular uptake and degradation. No cytochrome P450-mediated metabolism is involved; the compound has no classical drug-drug interaction profile through CYP enzymes [14].

5.4 Elimination

Plasma elimination half-life following intravenous bolus is approximately 0.36 hours (21 minutes), reflecting rapid distribution and proteolytic clearance. Following subcutaneous injection, the apparent elimination half-life is approximately 3 to 4 hours, the longer value reflecting absorption-rate-limited elimination (flip-flop kinetics). Renal clearance of intact somatropin is minimal (less than 0.1 percent of the injected dose is recovered intact in urine). Systemic clearance in healthy adults is approximately 14 to 17 L/hour, and in GHD adults approximately 8 to 12 L/hour [14, 29].

The pharmacodynamic half-life, measured as the duration of IGF-1 elevation following a single subcutaneous dose, is substantially longer than the plasma half-life of the parent molecule. Serum IGF-1 levels peak approximately 12 to 18 hours after injection and remain elevated above baseline for 18 to 28 hours, supporting the once-daily dosing schedule for standard somatropin products [31].

5.5 Special populations

Pediatric pharmacokinetics: Weight-based dosing produces comparable exposure across the pediatric age range. Clearance normalized to body weight is similar in children and adults.

Renal impairment: Moderate renal impairment does not substantially alter somatropin pharmacokinetics, as hepatic catabolism is the predominant clearance mechanism. In severe renal impairment (GFR less than 20 mL/min), clearance may be modestly reduced.

Hepatic impairment: No formal pharmacokinetic studies in hepatic impairment have been published. Hepatic catabolism is the predominant clearance route; significant hepatic dysfunction may prolong exposure.

Obesity: GH clearance is increased in obese individuals, and IGF-1 response to a given dose is blunted. Lean body weight-based dosing is recommended in obese patients to avoid supraphysiologic exposure from total body weight-based dosing [32].

5.6 Routes of administration

Subcutaneous injection: The standard route for all chronic indications. Administered once daily, typically in the evening to approximate the physiologic nocturnal GH secretory surge.

Intramuscular injection: An alternative route with slightly lower bioavailability and longer time to peak. Used infrequently in current practice.

Intravenous injection: Used only in pharmacokinetic research studies. Not employed in clinical therapy.

Weekly subcutaneous injection: Long-acting formulations (somapacitan, somatrogon, lonapegsomatropin) are administered by subcutaneous injection once weekly.

6. Clinical Evidence Base

6.1 Pediatric growth hormone deficiency

Pediatric GHD is the foundational indication for recombinant somatropin and the most extensively studied application. Multiple randomized controlled trials and large observational registries (KIGS, NCGS, GeNeSIS) have documented the efficacy and safety of daily subcutaneous somatropin at doses of 0.024 to 0.043 mg/kg/day in GHD children. Mean height velocity increases from pre-treatment rates of 3 to 4 cm/year to 8 to 12 cm/year during the first year of treatment. Mean adult height gains over the full treatment course (typically 3 to 10 years) range from 4 to 8 cm above predicted untreated height, with greater gains in patients who begin treatment at younger ages, who have more severe GHD, and who receive higher doses within the approved range [10, 11].

A systematic review and meta-analysis by Deodati and Cianfarani (2011) quantified the mean adult height gain attributable to GH treatment in GHD children at approximately 4 to 6 cm (approximately 1 standard deviation score) over untreated predicted height [33]. Response heterogeneity is substantial, and prediction models incorporating baseline height deficit, parental target height, GH dose, age at treatment initiation, and peak GH on stimulation testing have been developed to individualize therapy.

6.2 Turner syndrome

Somatropin at doses of 0.045 to 0.067 mg/kg/day (higher than the GHD dose to overcome the relative GH resistance in Turner syndrome) produces mean adult height gains of 5 to 8 cm in girls with Turner syndrome. The Rosenfeld et al. (1998) randomized controlled trial demonstrated a dose-response relationship with a mean final height gain of 5.0 cm at the lower dose and 8.4 cm at the higher dose compared to historical controls [34]. Treatment is typically initiated at diagnosis and continued until final height is achieved or until growth rate declines below 2 cm/year. Combination with low-dose oxandrolone has been studied for additional height gain.

6.3 Prader-Willi syndrome

Somatropin therapy in Prader-Willi syndrome targets both the growth failure and the body composition abnormalities (increased fat mass, reduced lean mass) characteristic of the condition. Treatment at 0.024 mg/kg/day produces increased height velocity, improved body composition with reduced fat mass and increased lean mass, improved motor development, and improved cognitive function in infants and children. The FDA approval (Genotropin, 2000) was based on two randomized controlled trials demonstrating these benefits [35]. Safety monitoring in Prader-Willi syndrome requires particular attention to respiratory function, as reports of sudden death in young children with Prader-Willi syndrome receiving GH therapy (particularly those with severe obesity, respiratory impairment, or obstructive sleep apnea) prompted a safety review and prescribing label warnings.

6.4 Small for gestational age

Children born small for gestational age who fail to achieve catch-up growth by age 2 to 4 years are approved for GH therapy at doses of 0.033 to 0.067 mg/kg/day. Randomized controlled trials demonstrate mean adult height gains of 3 to 6 cm above predicted untreated height, with response dependent on dose and duration of treatment [36].

6.5 Idiopathic short stature

The FDA approved somatropin (Humatrope) for idiopathic short stature (ISS) in 2003, defined as height more than 2.25 standard deviations below the mean with no identified etiology. Treatment produces mean adult height gains of 3 to 5 cm. The indication remains controversial; the Endocrine Society clinical practice guideline recommends consideration of GH therapy in ISS but acknowledges the modest effect size relative to cost [37].

6.6 Adult growth hormone deficiency

Adult GHD, whether continuing from childhood (transition patients) or developing de novo from pituitary tumors, surgery, radiation, or traumatic brain injury, produces a recognizable syndrome characterized by increased trunk fat mass, de-

creased lean body mass, reduced bone mineral density, unfavorable lipid profiles, decreased exercise capacity, impaired quality of life, and increased cardiovascular mortality [12, 13].

The Endocrine Society clinical practice guideline (Molitch et al. 2011, updated by Fleseriu et al. 2022) recommends GH replacement in adults with documented GHD on the basis of evidence from multiple randomized placebo-controlled trials demonstrating the following benefits [38]:

Body composition: Reduction of trunk fat mass by 8 to 16 percent and increase in lean body mass by 2 to 5 kg over 6 to 12 months of treatment. These changes are sustained with continued therapy.

Bone mineral density: Increase in lumbar spine and femoral neck bone mineral density by 3 to 8 percent over 18 to 24 months, with continued improvement over 5 to 10 years. Fracture risk reduction has been demonstrated in observational studies but not in randomized trials.

Lipid metabolism: Reduction in total cholesterol and LDL cholesterol by 5 to 15 percent, with variable effects on HDL cholesterol and triglycerides.

Quality of life: Improvement on validated instruments (QoL-AGHDA, NHP, SF-36) by 2 to 4 points over 6 to 12 months.

Cardiovascular risk markers: Reduction in C-reactive protein, improvement in endothelial function, and reduction in carotid intima-media thickness have been reported in controlled studies, though no randomized trial has demonstrated reduction in cardiovascular events.

Adult GH replacement is dosed by individualized titration, starting at 0.1 to 0.3 mg/day and adjusted at 4 to 8 week intervals based on serum IGF-1 levels (target: age- and sex-appropriate reference range), clinical response, and tolerability. Women, particularly those on oral estrogen therapy, require higher doses than men due to estrogen-mediated attenuation of hepatic GH sensitivity [39].

6.7 HIV-associated wasting and lipodystrophy

Serostim (somatropin) is FDA-approved for the treatment of HIV-associated wasting at doses of 0.1 mg/kg/day (up to 6 mg/day). Randomized controlled trials demonstrated increased lean body mass and body weight in patients with AIDS wasting

syndrome. Tesamorelin (Egrifta), a GHRH analog, is FDA-approved for reduction of excess abdominal fat in HIV-infected patients with lipodystrophy and is often preferred in this population because of a more targeted effect on visceral fat with a lower incidence of GH-related metabolic adverse events [40].

6.8 Short bowel syndrome

Zorbtive (somatropin) is FDA-approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support. GH enhances intestinal adaptation through trophic effects on enterocytes mediated by both direct GH action and IGF-1 [41].

6.9 Investigational and off-label applications

Anti-aging and age-related decline: The Rudman et al. (1990) study in the New England Journal of Medicine demonstrated that GH administration to healthy elderly men (0.03 mg/kg three times weekly for 6 months) increased lean body mass by 8.8 percent and decreased adipose tissue mass by 14.4 percent [42]. This landmark study initiated widespread interest in GH as an anti-aging therapy. Subsequent controlled trials have confirmed body composition changes in GH-sufficient elderly adults but have also demonstrated a high incidence of adverse events (edema, arthralgia, carpal tunnel syndrome, glucose intolerance) at the doses required to produce measurable body composition effects. A 2007 systematic review by Liu et al. in the Annals of Internal Medicine concluded that GH therapy in healthy elderly adults produces small changes in body composition (2 kg increase in lean mass, 2 kg decrease in fat mass) with frequent adverse events and no demonstrated functional benefit [43]. The Endocrine Society does not recommend GH therapy for age-related decline in GH secretion in the absence of documented GHD.

Athletic performance: Recombinant GH is prohibited by the World Anti-Doping Agency (WADA) in competitive sport. Controlled trials in young healthy adults demonstrate that GH administration increases lean body mass and reduces fat mass but does not improve aerobic capacity, strength, or exercise performance in GH-sufficient individuals [44].

Traumatic brain injury rehabilitation: TBI produces GHD in 10 to 30 percent of survivors. Uncontrolled studies suggest that GH replacement in TBI-associated GHD improves cognitive function and quality of life; randomized controlled data are limited [45].

7. Reported Research Dose Ranges

7.1 Approved pediatric doses

Growth hormone deficiency: 0.024 to 0.043 mg/kg/day subcutaneously (product-specific; Genotropin 0.024 mg/kg/day 6 to 7 days/week, Norditropin 0.024 to 0.034 mg/kg/day, Humatrope 0.026 mg/kg/day 6 days/week or 0.043 mg/kg/day 6 days/week divided).

Turner syndrome: 0.045 to 0.067 mg/kg/day.

Prader-Willi syndrome: 0.024 mg/kg/day (not to exceed 2.7 mg/day in children).

Small for gestational age: 0.033 to 0.067 mg/kg/day.

Idiopathic short stature: Up to 0.053 mg/kg/day.

SHOX deficiency: 0.05 mg/kg/day.

Chronic renal insufficiency: 0.035 mg/kg/day.

Noonan syndrome: Up to 0.066 mg/kg/day.

7.2 Approved adult doses

Adult GHD: Starting dose 0.1 to 0.3 mg/day (not weight-based), titrated upward by 0.1 to 0.2 mg/day at 4 to 8 week intervals based on IGF-1 levels and tolerability. Typical maintenance dose 0.2 to 0.8 mg/day. Women require higher doses than men. Patients over 60 years of age require lower doses.

HIV-associated wasting (Serostim): 0.1 mg/kg/day subcutaneously, up to 6 mg/day for 12 weeks.

Short bowel syndrome (Zorbtive): 0.1 mg/kg/day subcutaneously, up to 8 mg/day for 4 weeks.

7.3 Research dose ranges

Body composition optimization in GH-sufficient adults: 1 to 4 IU/day (approximately 0.33 to 1.33 mg/day), titrated based on IGF-1 monitoring and side-effect profile. These doses are off-label and not endorsed by endocrine societies for use in the absence of documented GHD.

Investigators should note that conversion between mass units and international units for recombinant somatropin is approximately 1 mg equals 3.0 IU (for products meeting current USP potency specifications).

8. Sourcing and Quality Verification

Pharmaceutical-grade somatropin is the only appropriate source for clinical and research applications. The compound is a complex recombinant protein requiring precise folding, disulfide bond formation, and stringent quality control that cannot be replicated by chemical suppliers offering small-molecule compounds.

Pharmaceutical products: FDA-approved somatropin products (Genotropin, Norditropin, Humatrope, Nutropin AQ, Omnitrope, Saizen, Zomacton) are manufactured under current Good Manufacturing Practice (cGMP) conditions and meet USP/EP specifications for identity, purity, potency, sterility, and endotoxin content. These products are available by prescription only and are subject to REMS or equivalent distribution controls in several jurisdictions.

Formulations: Products are supplied as either lyophilized powder requiring reconstitution (Genotropin, Humatrope vials, Saizen, Zomacton, Serostim, Zorbtive) or as liquid formulations in prefilled pens (Norditropin FlexPro, Nutropin AQ NuSpin, Omnitrope pens, Genotropin Miniquick). The liquid formulations contain preservatives (phenol or m-cresol) for multi-dose use.

Biosimilars: Omnitrope (Sandoz) was the first biosimilar somatropin approved in the United States (2006) and the European Union (2006). Additional biosimilars have been approved in various jurisdictions.

Verification considerations: Investigators acquiring somatropin from any source should verify: (1) Lot-specific certificate of analysis documenting identity (peptide mapping, mass spectrometry), purity (greater than 95 percent by reversed-phase HPLC, size exclusion chromatography for aggregates), potency (bioassay), sterility, and endotoxin content. (2) Cold chain documentation confirming uninterrupted refrigerated (2 to 8 degrees Celsius) storage from manufacture to receipt. (3) Intact tamper-evident packaging.

Counterfeit risk: The high cost and demand for somatropin, combined with its controlled-substance status and limited prescription access, have created a substantial counterfeit market. Counterfeit products may contain no active ingredient, sub-potent material, incorrect proteins, or microbial contaminants. Third-party an-

alytical testing through laboratories capable of protein characterization (mass spectrometry, bioassay) is strongly recommended for any product obtained outside of a verified pharmaceutical supply chain.

9. Reconstitution and Handling

9.1 Lyophilized products

Lyophilized somatropin products are reconstituted with the diluent provided by the manufacturer. Diluents vary by product: bacteriostatic water for injection containing 0.9 percent benzyl alcohol (multi-dose vials; contraindicated in neonates due to benzyl alcohol toxicity), sterile water for injection (single-use preparations), or manufacturer-specific diluent containing glycerin and/or m-cresol as preservative.

Reconstitution procedure: Direct the diluent stream against the glass wall of the vial, not directly onto the lyophilized cake. Swirl gently to dissolve; do not shake, as mechanical agitation causes protein aggregation, denaturation, and loss of biological activity. The reconstituted solution should be clear and colorless; discard if turbid, discolored, or containing particulate matter [46].

9.2 Liquid products

Prefilled pen formulations (Norditropin FlexPro, Omnitrope pens) are supplied as clear, colorless to slightly opalescent solutions ready for injection. No reconstitution is required.

9.3 Storage

Unreconstituted lyophilized products: Refrigerate at 2 to 8 degrees Celsius. Most products are stable at refrigerated temperature until the expiration date printed on the label (typically 18 to 36 months from manufacture). Some products (Genotropin Miniquick) may be stored at room temperature (up to 25 degrees Celsius) for up to 3 months before reconstitution.

Reconstituted lyophilized products: Refrigerate at 2 to 8 degrees Celsius. Use within 14 days (products reconstituted with bacteriostatic water) or within 24 hours (products reconstituted with sterile water for injection) of reconstitution.

Liquid pen products: Refrigerate at 2 to 8 degrees Celsius before first use. After first use, some products (Norditropin FlexPro) may be stored at room temperature (up to 25 degrees Celsius) for up to 21 days; others must remain refrigerated. Consult product-specific labeling.

9.4 General handling

Do not freeze. Do not expose to temperatures above 25 degrees Celsius for extended periods. Protect from light during storage. Do not use past the expiration date or the in-use stability period. Administer subcutaneous injection using sterile technique; rotate injection sites (abdomen, thigh, buttock, upper arm) to prevent lipohypertrophy.

10. Stack Interaction Considerations

Somatropin interacts with several compound classes through pharmacodynamic mechanisms related to the GH/IGF-1 axis, insulin signaling, and thyroid hormone metabolism. Investigators conducting research with somatropin in combination protocols should consider:

GH secretagogues (sermorelin, tesamorelin, CJC-1295, ipamorelin, GHRP-6, GHRP-2, ibutamoren/MK-677): Concurrent administration of exogenous somatropin with GH secretagogues that stimulate endogenous GH release is pharmacologically redundant at the pituitary level, as exogenous somatropin suppresses endogenous GH secretion through IGF-1-mediated negative feedback. Some research protocols employ secretagogues during periods off exogenous somatropin to support endogenous recovery, or use low-dose secretagogues concurrently to produce a more physiologic pulsatile GH profile superimposed on the exogenous baseline.

IGF-1 (mecasermin): Concurrent administration of somatropin and recombinant IGF-1 produces additive growth-promoting and hypoglycemic effects. The combination has been studied in severe primary IGF-1 deficiency (GH insensitivity syndromes) where GH alone is ineffective. Hypoglycemia risk is substantially increased with the combination.

Insulin: GH opposes insulin action on glucose disposal, producing insulin resistance that is dose-dependent and clinically significant at supraphysiologic GH levels. Patients with diabetes or prediabetes receiving somatropin require more frequent glucose monitoring and may require insulin dose adjustment. Some research protocols co-administer low-dose insulin with GH to mitigate the diabetogenic effect and to exploit the synergistic anabolic (protein-synthetic) actions of both hormones; this combination carries significant hypoglycemia risk and requires careful monitoring.

Thyroid hormone: GH increases the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by stimulating type 1 and type 2 iodothyronine deiodinase activity. Initiation of GH therapy can unmask central hypothyroidism (previously compensated by reduced T4-to-T3 conversion) or can increase levothyroxine dose requirements in patients already on thyroid replacement. Thyroid function should be monitored after GH initiation and at regular intervals during therapy [47].

Glucocorticoids: Supraphysiologic glucocorticoid exposure inhibits the GH/IGF-1 axis at multiple levels: it suppresses GHRH release, impairs GH secretion, induces hepatic GH resistance, and antagonizes IGF-1 action at the target tissue level. Concurrent glucocorticoid therapy reduces the efficacy of somatropin. Patients on hydrocortisone replacement for adrenal insufficiency should not exceed physiologic replacement doses during GH therapy [48].

Sex steroids: Oral estrogen reduces hepatic IGF-1 production through a first-pass hepatic effect, blunting the IGF-1 response to a given dose of GH. Women on oral estrogen therapy require higher GH doses; transdermal estrogen avoids the hepatic first-pass effect and is preferred during GH replacement. Testosterone enhances GH secretion and IGF-1 response and has synergistic anabolic effects with GH on body composition [39].

Aromatase inhibitors (in pediatric use): Combined GH and aromatase inhibitor therapy has been investigated to delay epiphyseal fusion and extend the growth period in boys with ISS. Efficacy data are mixed and the combination is not approved.

11. Adverse Events and Safety

11.1 Common adverse events

The adverse event profile of somatropin at approved replacement doses is well characterized from controlled trials and long-term registry data. The principal treatment-emergent adverse events are related to the fluid-retaining properties of GH and are dose-dependent [15, 16]:

- Peripheral edema (5 to 18 percent in adults, dose-dependent; less frequent in children)
- Arthralgia and joint stiffness (5 to 20 percent in adults)
- Myalgia (3 to 10 percent)
- Paresthesia (3 to 8 percent)
- Carpal tunnel syndrome (1 to 5 percent in adults; rare in children)
- Headache (common in children during the initial months of therapy)
- Injection site reactions (pain, erythema, lipoatrophy or lipohypertrophy; 2 to 5 percent)

These adverse events are more common in adults than in children, are more frequent at treatment initiation and during dose up-titration, and generally resolve with dose reduction or temporary discontinuation. Slow titration beginning at the lowest recommended dose minimizes fluid retention adverse events.

11.2 Metabolic adverse events

Insulin resistance and glucose intolerance: GH is a counter-regulatory hormone that opposes insulin action. Somatropin therapy produces dose-dependent insulin resistance, with increases in fasting glucose and fasting insulin levels. In children, clinically significant glucose intolerance is uncommon at approved doses. In adults, particularly those with pre-existing risk factors for diabetes (obesity, family history, impaired fasting glucose), GH therapy can precipitate overt glucose intolerance or type 2 diabetes. Monitoring of fasting glucose and HbA1c at baseline and every 6 to 12 months during therapy is recommended [49].

Lipid effects: At replacement doses, GH generally produces favorable lipid changes (reduction in LDL, variable effects on HDL and triglycerides). At supra-physiologic doses, lipid effects are less predictable.

11.3 Musculoskeletal adverse events

Slipped capital femoral epiphysis (SCFE): An increased incidence of SCFE has been reported in children receiving GH therapy, particularly in the context of rapid growth. The mechanism is likely related to GH-stimulated growth at the physis outpacing the structural strength of the growth plate. Patients developing hip or knee pain during GH therapy should be evaluated for SCFE.

Scoliosis progression: GH-stimulated rapid growth may accelerate scoliosis progression in predisposed individuals. Monitoring during therapy is recommended.

11.4 Neoplastic risk

The question of whether GH therapy increases the risk of de novo malignancy has been investigated extensively. The mechanistic concern arises from the mitogenic and anti-apoptotic properties of both GH and IGF-1 acting through the IGF-1R, and from epidemiological data associating high-normal IGF-1 levels with increased risk of prostate, breast, and colorectal cancer in the general population [50].

Long-term surveillance data from large registries (KIGS, HypoCCS, NordiNet IOS) encompassing tens of thousands of patient-years have not demonstrated a consistent increase in de novo malignancy risk in GH-treated patients without pre-existing risk factors. The French SAGhE (Sante Adulte GH Enfant) study reported an elevated standardized mortality ratio (SMR 1.33, 95 percent CI 1.08 to 1.64) in adults who had been treated with recombinant GH during childhood, driven predominantly by bone tumor and cardiovascular mortality in those who received higher doses (greater than 0.05 mg/kg/day); however, subsequent analyses from other countries (Sweden, Belgium, Netherlands) did not replicate the excess mortality finding [51, 52].

Somatropin is contraindicated in patients with active malignancy. In patients with a history of malignancy in remission, GH therapy may be considered after an appropriate disease-free interval; registry data do not demonstrate increased recurrence rates.

11.5 Intracranial hypertension

Benign intracranial hypertension (pseudotumor cerebri) has been reported rarely in children receiving GH therapy. Symptoms include headache, visual changes, nausea, and papilledema. The condition typically resolves with dose reduction or temporary discontinuation.

11.6 Prader-Willi syndrome-specific safety

Reports of sudden death in young children with Prader-Willi syndrome receiving GH therapy prompted FDA review and labeling changes. Risk factors include severe obesity (weight greater than 200 percent of ideal body weight), history of upper airway obstruction, respiratory impairment, or unidentified respiratory infections. Sleep studies and otolaryngologic evaluation are recommended before initiating GH therapy in Prader-Willi syndrome [53].

11.7 Immunogenicity

Anti-GH antibodies develop in a small percentage of patients (1 to 5 percent for somatropin, higher for the historical somatrem product). In most cases, the antibodies are low-titer and non-neutralizing and do not affect clinical response. Rarely, high-titer neutralizing antibodies produce growth attenuation.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative approaches to GH-axis modulation against recombinant somatropin, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators are GH-releasing hormone (GHRH) analogs and GH secretagogues that represent the principal non-somatropin strategies for GH-axis manipulation in research and clinical contexts.

12.1 Sermorelin (GRF 1-29)

Mechanism: Sermorelin is a synthetic 29-amino-acid peptide corresponding to the first 29 residues of the 44-amino-acid human growth hormone-releasing hormone (GHRH). It is the minimal biologically active fragment of GHRH and acts as a full agonist at the GHRH receptor on pituitary somatotropes, stimulating endogenous GH synthesis and pulsatile secretion [54].

Development trajectory: Sermorelin acetate (Geref) was FDA-approved in 1997 for the diagnostic evaluation of pituitary GH secretory capacity and for the treatment of idiopathic GH deficiency in children with growth failure. The product was voluntarily withdrawn from the market by EMD Serono in 2008, not for safety or efficacy reasons but due to limited commercial viability relative to direct somatropin therapy. Sermorelin remains available from compounding pharmacies.

Novelty: Low. The mechanism is well characterized and has been in clinical use for over 25 years.

Effect size: IGF-1 elevation and height velocity improvement in GHD children are consistently lower than those achieved with direct somatropin administration. Growth velocity increases of 4 to 6 cm/year (compared to 8 to 12 cm/year with somatropin) have been reported. Body composition effects in adults are modest and require longer treatment duration to become apparent.

Promising potential: Low to moderate. The compound is no longer commercially manufactured as an FDA-approved product but remains widely available through compounding and is used in clinical practice as a lower-cost, lower-risk alternative to somatropin for adult applications.

Side-effect profile: Favorable. The principal advantage of sermorelin over somatropin is that it stimulates endogenous GH release in physiologic pulses, preserving the normal feedback regulation and producing lower peak GH levels. Adverse events are predominantly injection-site reactions; fluid retention, arthralgia, and glucose intolerance are less frequent and less severe than with somatropin.

Overall validation: Moderate. FDA-approved (though withdrawn for commercial reasons), with a substantial clinical literature in both pediatric and adult applications.

Comparison to somatropin: Somatropin produces larger and more reliable IGF-1 elevation and clinical effect across all studied endpoints. Sermorelin offers the theoretical advantages of preserving pulsatile GH physiology and producing fewer dose-dependent adverse events, at the cost of lower efficacy and dependence on intact pituitary somatotrope function (ineffective in patients with pituitary destruction).

12.2 Tesamorelin (Egrifta)

Mechanism: Tesamorelin is a synthetic 44-amino-acid GHRH analog with a trans-3-hexenoic acid modification at the N-terminus that confers resistance to dipeptidyl peptidase IV (DPP-IV) cleavage and extends the biological half-life compared to native GHRH [55].

Development trajectory: FDA-approved in 2010 (Egrifta) for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Tesamorelin is the only GH-axis modulator other than somatropin with an active FDA-approved clinical indication.

Novelty: Moderate. The DPP-IV-resistant GHRH analog design is a meaningful pharmacokinetic improvement over sermorelin.

Effect size: In the pivotal Phase 3 trials, tesamorelin 2 mg/day subcutaneously produced a mean 15 percent reduction in visceral adipose tissue over 26 weeks, with concurrent increases in IGF-1 levels to the upper normal range. Trunk fat re-

duction is the best-documented effect; lean mass increases and lipid improvements have been reported but are more modest than those achieved with direct somatropin [56]. Effect is not sustained after discontinuation; visceral fat reaccumulates.

Promising potential: Moderate to high. Active commercial product with an FDA-approved indication. Investigational trials in non-HIV lipodystrophy and in NASH/MAFLD are ongoing.

Side-effect profile: Favorable relative to somatropin. Injection site reactions (erythema, pruritus) are the most common adverse events. Fluid retention effects are less frequent than with somatropin, likely due to the lower peak GH levels achieved through pulsatile endogenous secretion compared to bolus exogenous administration. Glucose tolerance effects are present but modest.

Overall validation: High. FDA-approved, with Phase 3 clinical trial data demonstrating visceral fat reduction in a specific population.

Comparison to somatropin: Tesamorelin produces more targeted visceral fat reduction with a better tolerability profile than somatropin at equivalent IGF-1 elevation. Somatropin produces broader effects (lean mass gain, bone density improvement, quality of life) that tesamorelin does not reliably achieve. The two compounds are complementary rather than interchangeable.

12.3 CJC-1295

Mechanism: CJC-1295 is a synthetic 30-amino-acid GHRH analog (modified GRF 1-29 with four amino acid substitutions for DPP-IV resistance) available in two forms: CJC-1295 without DAC (modified GRF 1-29, also known as Mod-GRF) and CJC-1295 with DAC (drug affinity complex), the latter containing a maleimidopropionic acid linker that forms a covalent bond with circulating albumin, extending the half-life from approximately 30 minutes to approximately 6 to 8 days [57].

Development trajectory: CJC-1295 with DAC was developed by ConjuChem Biotechnologies and advanced through Phase 2 clinical trials for adult GHD. In 2006, a Phase 2 study reported that single subcutaneous doses of 30 to 60 mcg/kg produced sustained GH and IGF-1 elevation for 6 to 14 days. The development program was discontinued following a death during clinical testing (the relationship to the study drug was not formally established). CJC-1295 has not received regulatory approval in any jurisdiction. It is available from compounding pharmacies and research peptide suppliers.

Novelty: Moderate. The albumin-binding DAC technology for half-life extension was novel at the time of development.

Effect size: Phase 2 data demonstrated a 46 to 58 percent increase in mean 24-hour GH secretion and a 45 to 75 percent increase in IGF-1 levels sustained for 6 to 14 days after a single dose (CJC-1295 with DAC) [57]. The modified GRF 1-29 form (without DAC) produces brief GH pulses similar to sermorelin, with IGF-1 elevation of 20 to 40 percent.

Promising potential: Low. Development discontinued. No regulatory approval. Available only through compounding and research supply channels.

Side-effect profile: Phase 2 data reported injection site reactions, transient flushing, and headache. The sustained GH elevation produced by the DAC form raises theoretical concerns about prolonged insulin resistance; these have not been characterized in long-term studies.

Overall validation: Low. Phase 2 data only, with a discontinued development program and a safety signal (death during clinical testing).

Comparison to somatropin: CJC-1295 with DAC produces sustained GH and IGF-1 elevation approaching the magnitude of daily somatropin, with the convenience of less-frequent dosing. The absence of regulatory approval, the limited safety database, and the discontinued development program place it substantially below somatropin in overall validation. CJC-1295 without DAC (Mod-GRF) produces effects comparable to sermorelin and shares its limitations.

12.4 Ipamorelin

Mechanism: Ipamorelin is a synthetic pentapeptide (Aib-His-D-2Nal-D-Phe-Lys-NH₂) growth hormone secretagogue that acts as a selective agonist at the growth hormone secretagogue receptor type 1a (GHS-R1a, the ghrelin receptor) on pituitary somatotropes and hypothalamic neurons. Ipamorelin is distinguished from earlier GH secretagogues (GHRP-6, GHRP-2, hexarelin) by its high selectivity for GH release without significant stimulation of cortisol, prolactin, or ACTH [58].

Development trajectory: Developed by Novo Nordisk and advanced through Phase 2 clinical trials in postoperative ileus and in growth hormone-related indications. The postoperative ileus program (in combination with other agents) did not

produce positive Phase 3 results. Ipamorelin has not received regulatory approval for any indication. It is widely available from compounding pharmacies and research peptide suppliers, often in combination with CJC-1295 without DAC.

Novelty: Moderate. The high GH selectivity without cortisol or prolactin stimulation distinguishes it from earlier secretagogues.

Effect size: Subcutaneous ipamorelin at doses of 1 to 3 mcg/kg produces GH pulses of 2 to 5-fold above baseline, with peak effect at 30 to 60 minutes and duration of approximately 2 hours. IGF-1 elevation with chronic dosing (typically 200 to 300 mcg two to three times daily) is approximately 15 to 30 percent, substantially lower than the IGF-1 elevation achievable with replacement-dose somatropin.

Promising potential: Low to moderate. No regulatory approval, but wide availability through compounding and a large empirical user base.

Side-effect profile: Favorable. The GH selectivity minimizes cortisol and prolactin stimulation. Adverse events in clinical trials were minimal (transient warmth at injection site, mild headache). The brief GH pulse minimizes sustained insulin resistance.

Overall validation: Low. Phase 2 data in non-GH indications. No GH-specific registration data. Empirical use is extensive but uncontrolled.

Comparison to somatropin: Ipamorelin produces substantially lower GH and IGF-1 elevation than somatropin and is not a replacement for somatropin in documented GHD. It is used in research and off-label contexts as a lower-risk, lower-efficacy GH-axis stimulant, often in combination with CJC-1295 without DAC to produce synergistic GH release through dual GHRH receptor and GHS receptor activation.

12.5 Ibutamoren (MK-677)

Mechanism: Ibutamoren (MK-677) is a non-peptide, orally active growth hormone secretagogue that acts as a selective agonist at the GHS-R1a (ghrelin receptor). It increases GH secretion through both direct pituitary action and hypothalamic GHRH neuron activation, and suppresses somatostatin tone. Unlike peptide secretagogues, ibutamoren is orally bioavailable with a long plasma half-life (approximately 4 to 6 hours), supporting once-daily oral dosing [59].

Development trajectory: Developed by Merck. Extensive Phase 2 clinical trials were conducted in multiple populations: elderly adults (Murphy et al. 2001; Nass et al. 2008), hip fracture patients (Bach et al. 2004), obese males (Svensson et al. 1998), and GHD adults. The compound consistently produced sustained GH and IGF-1 elevation (40 to 80 percent increase in IGF-1 from baseline) with once-daily oral dosing at 25 mg [60, 61]. Despite these pharmacodynamic results, Merck did not advance ibutamoren to Phase 3 registration trials for any indication. The compound has not received regulatory approval.

Novelty: High. Oral bioavailability and non-peptide GH secretagogue activity are unique in this comparator landscape.

Effect size: IGF-1 elevation of 40 to 80 percent is the highest among the secretagogue comparators and approaches the lower end of the somatropin replacement range. In the Nass et al. (2008) 2-year study in elderly adults, ibutamoren 25 mg daily restored mean IGF-1 levels to young-adult reference range values. Body composition effects (increased lean mass, decreased fat mass) were reported but modest compared to somatropin [61].

Promising potential: Moderate. No regulatory approval and development discontinued by Merck. Widely available as a research chemical. The oral route of administration is a significant practical advantage.

Side-effect profile: Appetite stimulation (ghrelin receptor agonism), mild edema, transient muscle pain, and modest increases in fasting glucose have been reported. The Nass et al. (2008) 2-year study reported no serious adverse events but did report an increase in fasting glucose (mean 0.3 mmol/L) and HbA1c (mean 0.1 percent) [61]. The sustained GH elevation and appetite stimulation may be disadvantageous in obese or diabetic populations.

Overall validation: Moderate. Extensive Phase 2 data across multiple populations, with consistent pharmacodynamic (GH and IGF-1 elevation) and modest clinical (body composition) effects. The absence of Phase 3 registration data limits the validation level.

Comparison to somatropin: Ibutamoren is the most convenient (oral, once-daily) GH-axis modulator in this comparator panel and produces the highest IGF-1 elevation among the secretagogues. It does not achieve the full magnitude of GH replacement provided by somatropin at standard doses and lacks regulatory approval

for any indication. The oral route and the sustained physiologic-range IGF-1 elevation make it a potential complement to, rather than replacement for, somatropin in research contexts.

12.6 Comparator summary

The five comparators occupy distinct positions in the GH-axis modulation landscape. **Sermorelin** is the historical reference GHRH analog with FDA-approval history but modest efficacy relative to somatropin. **Tesamorelin** is the only comparator with an active FDA-approved indication and produces targeted visceral fat reduction with a favorable side-effect profile. **CJC-1295** (particularly the DAC form) offers sustained GH elevation with less frequent dosing but has a discontinued development program and limited safety data. **Ipamorelin** is a highly selective GH secretagogue with minimal non-GH hormonal effects, used primarily in combination protocols. **Ibutamoren** is the only oral agent and produces the highest IGF-1 elevation among the secretagogues, with extensive Phase 2 but no Phase 3 data.

Recombinant somatropin occupies the reference position in this comparator landscape: it is the only compound with broad regulatory approval across multiple pediatric and adult indications, the most extensive safety database (over 40 years of postmarketing surveillance), the highest efficacy for all GH-dependent endpoints (growth, body composition, bone density, IGF-1 normalization), and the most complete clinical evidence base. Its principal limitations relative to the comparators are the requirement for daily injection (addressed by long-acting formulations), the higher incidence of dose-dependent adverse events (fluid retention, insulin resistance), the suppression of endogenous GH pulsatility, and the cost (substantially higher than secretagogue alternatives).

For investigators evaluating GH-axis modulation strategies, the choice between somatropin and the comparators depends on the endpoint of interest, the population, and the risk-benefit calculation. Documented GHD in children or adults requires somatropin (or a long-acting formulation) as the standard of care. Body composition optimization in GH-sufficient populations may favor a secretagogue approach (tesamorelin for visceral fat, ipamorelin/CJC-1295 combination for pulsatile GH support, ibutamoren for oral convenience) that preserves endogenous GH regulation and produces fewer adverse events at the cost of lower maximal efficacy.

13. References

1. Chen EY, Liao YC, Smith DH, et al. The human growth hormone locus: nucleotide sequence, biology, and evolution. *Genomics*. 1989;4(4):479-497.
2. Bewley TA, Li CH. Circular dichroism and CD studies on human pituitary growth hormone and its derivatives. *Biochemistry*. 1972;11(5):884-888.
3. de Vos AM, Ultsch M, Kossiakoff AA. Human growth hormone and extracellular domain of its receptor: crystal structure of the complex. *Science*. 1992;255(5042):306-312.
4. Baumann G. Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr Rev*. 1991;12(4):424-449.
5. Pavlovic M, Girardin E, Kapetanovic L, Ho K, Trouvin JH. Similar biological medicinal products containing recombinant human growth hormone: European regulation. *Horm Res*. 2008;69(1):14-21.
6. Brooks AJ, Waters MJ. The growth hormone receptor: mechanism of activation and clinical implications. *Nat Rev Endocrinol*. 2010;6(9):515-525.
7. Herrington J, Smit LS, Schwartz J, Carter-Su C. The role of STAT proteins in growth hormone signaling. *Oncogene*. 2000;19(21):2585-2597.
8. Raben MS. Treatment of a pituitary dwarf with human growth hormone. *J Clin Endocrinol Metab*. 1958;18(8):901-903.
9. Ayyar VS. History of growth hormone therapy. *Indian J Endocrinol Metab*. 2011;15(Suppl 3):S162-S165.
10. Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. *BMJ*. 2011;342:c7157.
11. Ranke MB, Lindberg A, Ferrandez Longas A, et al. Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatr Res*. 2007;61(1):105-110.

12. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(6):1587-1609.
13. Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency: benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne)*. 2013;4:64.
14. Laursen T, Gravholt CH, Heickendorff L, et al. Long-term effects of continuous subcutaneous infusion versus daily subcutaneous injections of growth hormone (GH) on the insulin-like growth factor system, insulin sensitivity, body composition, and bone and lipoprotein metabolism in GH-deficient adults. *J Clin Endocrinol Metab*. 2001;86(3):1222-1228.
15. Abs R, Bengtsson BA, Hernberg-Stahl E, et al. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clin Endocrinol (Oxf)*. 1999;50(6):703-713.
16. Stochholm K, Johannsson G. Reviewing the safety of GH replacement therapy in adults. *Growth Horm IGF Res*. 2015;25(4):149-157.
17. Brown P, Brandel JP, Sato T, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. *Emerg Infect Dis*. 2012;18(6):901-907.
18. Hintz RL. The prismatic case of Creutzfeldt-Jakob disease associated with pituitary growth hormone treatment. *J Clin Endocrinol Metab*. 1995;80(8):2298-2301.
19. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr*. 2003;143(4):415-421.
20. Miller BS, Blair JC, Rasmussen MH, et al. Weekly somapacitan is effective and well tolerated in children with GH deficiency: the randomized Phase 3 REAL4 trial. *J Clin Endocrinol Metab*. 2022;107(12):3378-3388.
21. Wells JA, de Vos AM. Hematopoietic receptor complexes. *Annu Rev Biochem*. 1996;65:609-634.
22. Zhu T, Goh EL, Graichen R, Ling L, Lobie PE. Signal transduction via the growth hormone receptor. *Cell Signal*. 2001;13(9):599-616.

23. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev.* 2009;30(2):152-177.
24. Baxter RC. Insulin-like growth factor binding proteins in the human circulation: a review. *Horm Res.* 1994;42(4-5):140-144.
25. Le Roith D, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis: 2001. *Endocr Rev.* 2001;22(1):53-74.
26. Moller N, Vendelbo MH, Kampmann U, et al. Growth hormone and protein metabolism. *Clin Nutr.* 2009;28(6):597-603.
27. Moller J, Frandsen E, Fisker S, Jorgensen JO, Christiansen JS. Decreased plasma and extracellular volume in growth hormone deficient adults and the acute and prolonged effects of GH administration: a controlled experimental study. *Clin Endocrinol (Oxf).* 1996;44(5):533-539.
28. Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G. Dual defects in pulsatile growth hormone secretion and clearance subserve the hypsomatotropism of obesity in man. *J Clin Endocrinol Metab.* 1991;72(1):51-59.
29. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology: drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.
30. Baumann G, Shaw MA, Amburn K. Regulation of plasma growth hormone-binding proteins in health and disease. *Metabolism.* 1989;38(7):683-689.
31. Jorgensen JO, Moller N, Lauritzen T, Alberti KG, Orskov H, Christiansen JS. Evening versus morning injections of growth hormone (GH) in GH-deficient patients: effects on 24-hour patterns of circulating hormones and metabolites. *J Clin Endocrinol Metab.* 1990;70(1):207-214.
32. Savastano S, di Somma C, Barrea L, Colao A. The complex relationship between obesity and the somatotrophic axis: the long and winding road. *Growth Horm IGF Res.* 2014;24(6):221-226.
33. Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. *BMJ.* 2011;342:c7157.
34. Rosenfeld RG, Attie KM, Frane J, et al. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. *J Pediatr.* 1998;132(2):319-324.

35. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab.* 2002;87(4):1581-1585.
36. Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. *Pediatrics.* 2009;124(3):e519-e531.
37. Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab.* 2008;93(11):4210-4217.
38. Fleseriu M, Hashim IA, Engel SS, et al. Updated guidelines for diagnosis and treatment of adult GH deficiency. *J Clin Endocrinol Metab.* 2022;107(11):e4251-e4264.
39. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev.* 1998;19(6):717-797.
40. Falutz J, Allas S, Blot K, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med.* 2007;357(23):2359-2370.
41. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. *Gastroenterology.* 2003;124(2):293-302.
42. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med.* 1990;323(1):1-6.
43. Liu H, Bravata DM, Olkin I, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med.* 2007;146(2):104-115.
44. Meinhardt U, Nelson AE, Hansen JL, et al. The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med.* 2010;152(9):568-577.
45. Moreau OK, Cortet-Rudelli C, Yollin E, Merlen E, Daveluy W, Rousseaux M. Growth hormone replacement therapy in patients with traumatic brain injury. *J Neurotrauma.* 2013;30(12):998-1006.
46. Genotropin prescribing information. Pfizer Inc. Revised 2023.

47. Porretti S, Giavoli C, Ronchi C, et al. Recombinant human GH replacement therapy and thyroid function in a large group of adult GH-deficient patients: when does L-T(4) therapy become mandatory? *J Clin Endocrinol Metab.* 2002;87(5):2042-2045.
48. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev.* 2008;29(5):535-559.
49. Cutfield WS, Wilton P, Bennmarker H, et al. Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet.* 2000;355(9204):610-613.
50. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet.* 2004;363(9418):1346-1353.
51. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J Clin Endocrinol Metab.* 2012;97(2):416-425.
52. Savendahl L, Maes M, Albertsson-Wikland K, et al. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, the Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *J Clin Endocrinol Metab.* 2012;97(2):E213-E217.
53. Deal CL, Tony M, Hoybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2013;98(6):E1072-E1087.
54. Prakash A, Goa KL. Sermorelin: a review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency. *BioDrugs.* 1999;12(2):139-157.
55. Dhillon S. Tesamorelin: a review of its use in the management of HIV-associated lipodystrophy. *Drugs.* 2011;71(8):1071-1091.
56. Falutz J, Mamputu JC, Potvin D, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, dou-

ble-blind placebo-controlled Phase 3 trials with safety extension data. J Clin Endocrinol Metab. 2010;95(9):4291-4304.

57. Teichman SL, Neale A, Lawrence B, Gagnon C, Castaigne JP, Bhatt R. Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults. J Clin Endocrinol Metab. 2006;91(3):799-805.
58. Raun K, Hansen BS, Johansen NL, et al. Ipamorelin, the first selective growth hormone secretagogue. Eur J Endocrinol. 1998;139(5):552-561.
59. Patchett AA, Nargund RP, Tata JR, et al. Design and biological activities of L-163,191 (MK-0677): a potent, orally active growth hormone secretagogue. Proc Natl Acad Sci U S A. 1995;92(15):7001-7005.
60. Murphy MG, Plunkett LM, Gertz BJ, et al. MK-677, an orally active growth hormone secretagogue, reverses diet-induced catabolism. J Clin Endocrinol Metab. 1998;83(2):320-325.
61. Nass R, Pezzoli SS, Oliveri MC, et al. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Med. 2008;149(9):601-611.

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