

Somatrogon

A long-acting glycoprotein fusion of recombinant human growth hormone with three copies of the C-terminal peptide of human chorionic gonadotropin beta-subunit, engineered by OPKO Health and commercialized by Pfizer as a once-weekly subcutaneous injection for the treatment of pediatric growth hormone deficiency, distinguished from daily somatropin by its prolonged pharmacokinetic profile and from other long-acting growth hormone preparations by its CTP-based half-life extension platform.

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ABSTRACT

Somatrogon (somatrogon-ghla; CAS 1663481-09-1; approximate molecular weight 40 kDa including glycosylation) is a long-acting recombinant human growth hormone receptor agonist produced in Chinese hamster ovary cells by recombinant DNA technology and approved for the treatment of pediatric growth hormone deficiency as a once-weekly subcutaneous injection. The molecule comprises the complete 191-amino-acid sequence of native human growth hormone with one copy of the 28-amino-acid C-terminal peptide (CTP) from the beta-subunit of human chorionic gonadotropin fused at the N-terminus and two tandem copies of CTP fused at the C-terminus [1, 2]. The CTP cassettes introduce O-linked glycosylation sites that reduce renal clearance, extend the circulating half-life from the 2 to 4 hours of native somatotropin to an effective half-life of approximately 28 to 38 hours, and thereby permit once-weekly dosing at 0.66 mg/kg without loss of growth-promoting efficacy relative to daily somatotropin [3, 4]. Somatrogon binds the homodimeric growth hormone receptor and activates the JAK2-STAT5b signaling cascade, producing downstream increases in hepatic and peripheral insulin-like growth factor 1 (IGF-1) synthesis, skeletal longitudinal growth, protein anabolism, and modulation of carbohydrate and lipid metabolism identical in pathway to native growth hormone [5, 6]. The pivotal global Phase 3 clinical trial (NCT02968004) randomized 224 treatment-naive prepubertal children with growth hormone deficiency to once-weekly somatrogon (0.66 mg/kg) or once-daily somatotropin (Genotropin, 0.24 mg/kg/week) for 12 months and demonstrated non-inferiority of somatrogon on the primary endpoint of annualized height velocity (somatrogon 10.12 cm/year versus

somatropin 9.78 cm/year), with height standard deviation score improvements numerically favoring the somatrogon arm [7]. A parallel Phase 3 study in Japanese children confirmed non-inferiority with consistent safety [8]. Long-term extension data through 5 years of treatment demonstrated sustained catch-up growth with a mean height standard deviation score increase from baseline of 1.94 at extension year 4, consistent with durable efficacy [9]. The safety profile is characterized by injection site reactions (pain in 39.4 percent of somatrogon recipients versus 25.2 percent of somatropin recipients), nasopharyngitis, headache, pyrexia, and the pharmacological class effects of growth hormone therapy including transient hyperglycemia, hypothyroidism unmasking, and benign intracranial hypertension [7, 10]. Immunogenicity is notable: 77.1 percent of somatrogon-treated subjects developed anti-drug antibodies during the 12-month pivotal trial versus 15.6 percent of somatropin-treated subjects, but neutralizing antibody activity was not detected, and anti-drug antibodies did not have a clinically significant impact on efficacy or safety through 42 months of observation [7, 11]. Somatrogon received marketing authorization from the European Medicines Agency in January 2022, from Health Canada in December 2021, from the Australian Therapeutic Goods Administration in 2021, and from the United States Food and Drug Administration on June 27, 2023, following an initial complete response letter in January 2022 that required supplementary manufacturing data [12, 13]. The compound is marketed as Ngenla in a prefilled pen presentation requiring no reconstitution. This monograph reviews the molecular design, CTP-based half-life extension technology, growth hormone receptor pharmacology, comprehensive pharmacokinetic characterization, the pediatric clinical evidence base, sourcing and handling considerations, drug

interaction profile, adverse event and immunogenicity data, and a structured comparative assessment of five alternative growth hormone preparations against somatrogen on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Somatrogon.

United States Adopted Name: Somatrogon-ghla. The suffix -ghla is the nonproprietary name distinguishing suffix assigned by the FDA under the Biologics Price Competition and Innovation Act naming convention for biological products [12].

Marketed name: Ngenla (Pfizer). The brand name is used in all approved jurisdictions including the European Union, Canada, Australia, Japan, and the United States.

Development codes: MOD-4023 (OPKO Health). The development code is the canonical identifier in the early clinical pharmacology literature and in the Phase 1 and Phase 2 clinical trial publications [14, 15].

Chemical Abstracts Service registry number: 1663481-09-1.

UNII (Unique Ingredient Identifier): 6D848RA61B (FDA Substance Registration System).

Structural description: Somatrogon is a glycoprotein consisting of the 191-amino-acid sequence of human growth hormone (somatropin) with one copy of the 28-amino-acid C-terminal peptide (CTP) of the beta-subunit of human chorionic gonadotropin appended at the N-terminus and two tandem copies of the same CTP appended at the C-terminus, for a total polypeptide chain of approximately 275 amino acids before glycosylation [1, 2].

1.2 Structural class and chemistry

Somatrogon is a recombinant glycoprotein hormone analog classified as a long-acting growth hormone receptor agonist. The structural class places it within the engineered growth hormone family, a group of modified somatropin derivatives designed to extend pharmacokinetic half-life beyond the 2 to 4 hours of native growth hormone and thereby reduce injection frequency from daily to weekly or less frequent administration [16].

Molecular formula (aglycosylated polypeptide): C1359H2125N361O420S7.

Molecular weight (aglycosylated): Approximately 30,465 Da.

Apparent molecular weight (glycosylated): Approximately 40 kDa. The difference between the polypeptide mass and the apparent molecular weight reflects the O-linked glycosylation contributed by the CTP domains [1, 2].

Physical properties: Clear to slightly opalescent, colorless to slightly yellow solution in the commercial prefilled pen presentation. The protein is formulated in a phosphate-buffered solution with poloxamer 188 as a stabilizer. Somatrogen is not supplied as a lyophilized powder; the prefilled pen requires no reconstitution [17].

Glycosylation: The CTP domains contain four O-linked glycosylation sites per copy (serine residues within the CTP sequence that are substrates for CHO cell O-glycosyltransferases). The glycan structures are predominantly core-1 type sialylated O-glycans. The sialylation increases the hydrodynamic radius of the molecule, reduces glomerular filtration, and is the principal molecular basis for the extended circulating half-life [1, 2, 18].

Disulfide bonds: Somatrogen retains the two disulfide bonds of native human growth hormone (Cys53-Cys165 and Cys182-Cys189 in the growth hormone numbering) that are essential for the four-helix bundle tertiary structure and growth hormone receptor binding. The CTP domains do not contain cysteine residues and do not contribute disulfide bonds.

1.3 Manufacture

Somatrogen is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. The expression construct encodes the CTP-hGH-CTP-CTP fusion protein under the control of a mammalian promoter. The CHO cell line provides the mammalian O-linked glycosylation machinery required for proper glycosylation of the CTP domains [1, 19]. Production follows standard recombinant glycoprotein manufacturing: cell culture in bioreactors, harvest of conditioned medium, multi-step chromatographic purification (typically including ion exchange, hydrophobic interaction, and size exclusion chromatography), viral inactivation and filtration, and formulation into the final drug product. The manufacturing process was the subject of the FDA complete response letter issued in January 2022; the re-submitted biologics license application addressed manufacturing-related concerns and was approved in June 2023 [12, 13].

2. Abstract

Somatrogon (MOD-4023; Ngenla; somatrogon-ghla) is a long-acting recombinant human growth hormone receptor agonist engineered by fusion of the 191-amino-acid human growth hormone sequence with three copies of the 28-amino-acid C-terminal peptide (CTP) from the beta-subunit of human chorionic gonadotropin (one N-terminal, two C-terminal in tandem), produced in Chinese hamster ovary cells, and approved for once-weekly subcutaneous injection in pediatric patients with growth hormone deficiency in the European Union (January 2022), Canada (December 2021), Australia (2021), Japan (2022), and the United States (June 27, 2023) [1, 7, 12].

The CTP-based half-life extension technology, developed by OPKO Health (formerly Prolor Biotech) and licensed to Pfizer in a 2014 worldwide development and commercialization agreement, exploits the natural O-linked glycosylation of the CTP domain to increase hydrodynamic radius and reduce renal clearance of the attached growth hormone moiety without chemical modification, PEGylation, albumin fusion, or encapsulation [1, 2, 18]. The approach preserves the native growth hormone amino acid sequence and receptor binding interface while extending the effective half-life from the 2 to 4 hours of daily somatropin to approximately 28 to 38 hours, permitting once-weekly dosing at 0.66 mg/kg subcutaneously [3, 4].

The pharmacological mechanism is identical in pathway to native growth hormone: somatrogon binds the homodimeric growth hormone receptor (GHR) on hepatocytes, chondrocytes, adipocytes, and other target cells, triggering receptor dimerization, activation of the associated Janus kinase 2 (JAK2), phosphorylation of signal transducer and activator of transcription 5b (STAT5b), and transcriptional induction of insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP-3) [5, 6]. The downstream physiological consequences include longitudinal skeletal growth through chondrocyte proliferation and differentiation in the epiphyseal growth plate, stimulation of protein synthesis, lipolysis, and modulation of carbohydrate metabolism including transient insulin resistance.

The pivotal Phase 3 clinical program comprised a global multicenter randomized active-controlled trial in 224 treatment-naïve prepubertal children with confirmed growth hormone deficiency (NCT02968004) and a parallel Phase 3 trial in 49 Japanese children (NCT03874013) [7, 8]. Both trials demonstrated non-inferiority of

once-weekly somatrogen to once-daily somatropin (Genotropin) on annualized height velocity at 12 months. The global trial reported annualized height velocity of 10.12 cm/year in the somatrogen arm versus 9.78 cm/year in the somatropin arm, with the lower bound of the 95 percent confidence interval for the treatment difference exceeding the prespecified non-inferiority margin of negative 1.8 cm/year [7]. Height standard deviation score improvements were numerically greater in the somatrogen arm at all time points through 12 months. Open-label extension data through 5 years confirmed sustained efficacy with continued catch-up growth and a mean height standard deviation score increase from baseline of 1.94 at extension year 4 [9].

The safety profile in the pivotal trials was generally consistent with the known pharmacological effects of growth hormone therapy. Injection site reactions were the most frequent adverse events, with injection site pain reported by 39.4 percent of somatrogen recipients versus 25.2 percent of somatropin recipients; injection site erythema and pruritus were observed only in the somatrogen arm [7, 10]. Other common adverse events included nasopharyngitis, headache, pyrexia, anemia, cough, and vomiting. Growth hormone class effects including transient hyperglycemia, unmasking of central hypothyroidism, and rare benign intracranial hypertension were observed at rates consistent with daily somatropin [10]. Immunogenicity was notable: 77.1 percent of somatrogen-treated subjects developed anti-drug antibodies versus 15.6 percent of somatropin-treated subjects, but no neutralizing antibodies were detected, and no clinically significant impact on efficacy or safety was observed through 42 months of follow-up [7, 11].

This monograph reviews the molecular design and CTP technology, growth hormone receptor pharmacology, pharmacokinetics, the preclinical evidence base, the complete clinical trial program, sourcing and handling, drug interactions, adverse events and immunogenicity, and a comparative assessment of five alternative growth hormone preparations (somapacitan, lonapegsomatropin, daily somatropin, somatorelin, and tesamorelin) against somatrogen on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 CTP technology origin

The C-terminal peptide (CTP) technology was developed by Prolor Biotech (later acquired by OPKO Health in 2013) based on the observation that the beta-subunit of human chorionic gonadotropin (hCG) has an unusually long circulating half-life among peptide hormones, attributable to the 28-amino-acid CTP domain at its C-terminus that contains four O-linked glycosylation sites [1, 2]. The sialylated O-glycans on the CTP domain increase the hydrodynamic radius of the molecule and shield it from renal filtration, producing a half-life approximately 5- to 10-fold longer than the corresponding unmodified peptide. The approach was initially validated with follicle-stimulating hormone (corifollitropin alfa, developed by Organon/MSD using a similar CTP concept) and was subsequently applied to human growth hormone by Prolor Biotech as MOD-4023 [18].

The CTP platform is distinguished from other half-life extension technologies applied to growth hormone (PEGylation for lonapegsomatropin, albumin binding for somapacitan, non-covalent albumin binding for somavaratan, sustained-release microsphere encapsulation for LB03002) by the fact that the modification uses a naturally occurring human peptide sequence rather than a synthetic polymer or chemical linker [16, 20]. The CTP does not alter the growth hormone amino acid sequence, does not introduce non-human elements, and does not require chemical conjugation steps that could impair receptor binding or introduce heterogeneity.

3.2 Preclinical and early clinical development

OPKO Health (as Prolor Biotech) conducted the initial preclinical characterization of MOD-4023 in rodent and primate models. Preclinical studies demonstrated that MOD-4023 activated the growth hormone receptor with potency comparable to native somatotropin, produced dose-dependent increases in circulating IGF-1 in hypophysectomized rats, and promoted tibial growth in the classical rat tibia bioassay at weekly doses equivalent to the total weekly dose of daily somatotropin [14, 18]. The

extended pharmacokinetic profile was confirmed in rodents and cynomolgus monkeys, with terminal half-lives approximately 5- to 10-fold longer than native somatropin.

A Phase 1 single-ascending-dose study in healthy adult volunteers (NCT01004107) characterized the pharmacokinetic profile of somatrogen administered as single subcutaneous injections at doses of 0.5 to 15 mg [14]. The study demonstrated dose-proportional pharmacokinetics, a mean terminal half-life of approximately 18.2 hours at the 15 mg dose, time to peak plasma concentration of approximately 10 hours, and dose-dependent increases in serum IGF-1 lasting approximately 4 to 5 days.

A Phase 2 dose-finding study in 64 prepubertal children with growth hormone deficiency previously treated with daily somatropin (NCT01592500) evaluated three once-weekly somatrogen doses (0.25, 0.48, and 0.66 mg/kg) against once-daily Genotropin for 12 months [15]. The 0.66 mg/kg/week dose produced annualized height velocity (11.9 cm/year) comparable to daily somatropin (12.5 cm/year) and was selected as the Phase 3 dose. The two lower doses produced lower but still clinically meaningful height velocity, establishing a dose-response relationship.

3.3 OPKO-Pfizer partnership

In November 2014, OPKO Health and Pfizer entered a worldwide agreement for the development and commercialization of somatrogen [19]. Under the agreement, OPKO was responsible for conducting the Phase 3 clinical program and Pfizer was responsible for regulatory registration and global commercialization. The partnership reflected the complementary strengths of the CTP technology platform (OPKO) and the established growth hormone commercial infrastructure (Pfizer, the manufacturer of Genotropin).

3.4 Regulatory history

The biologics license application was submitted to the FDA in March 2020 and accepted for review in June 2020. The FDA extended the review period in September 2021 to evaluate additional manufacturing data. In January 2022, the FDA issued a complete response letter (CRL) citing concerns related to manufacturing controls at

a third-party facility; the CRL did not raise efficacy or safety objections [12, 13]. Pfizer resubmitted the BLA addressing the manufacturing concerns, and the FDA approved Ngenla on June 27, 2023.

In parallel, the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion in December 2021, and the European Commission granted marketing authorization in January 2022. Health Canada approved Ngenla in December 2021. The Australian Therapeutic Goods Administration approved the compound in 2021. The Japanese Pharmaceuticals and Medical Devices Agency approved the compound in 2022 [12].

3.5 Adult growth hormone deficiency

A Phase 3 randomized trial of somatrogon in adults with growth hormone deficiency was initiated and has reported results demonstrating efficacy in maintaining IGF-1 levels and favorable tolerability [21]. As of this monograph revision, the adult indication has not received regulatory approval in any jurisdiction.

4. Mechanism of Action

Somatrogen is a growth hormone receptor agonist. Its mechanism of action is identical in pathway to native human growth hormone (somatropin) and is mediated through binding to and activation of the homodimeric growth hormone receptor, a class 1 cytokine receptor expressed on hepatocytes, chondrocytes, osteoblasts, adipocytes, myocytes, and lymphocytes.

4.1 Growth hormone receptor binding and activation

The growth hormone receptor (GHR) is a single-pass transmembrane glycoprotein that exists as a preformed homodimer on the cell surface [5, 6]. Growth hormone binds the GHR homodimer through two distinct binding sites on the growth hormone molecule (Site 1 and Site 2) that engage two receptor molecules sequentially: Site 1 binds the first GHR protomer with high affinity (K_d approximately 1 nM), and Site 2 binds the second protomer with lower affinity, producing the ternary 1:2 hormone-receptor complex that is the signaling-competent form [5].

Somatrogen preserves the native growth hormone amino acid sequence including both receptor binding sites. The CTP fusions at the N-terminus and C-terminus are positioned at the termini of the four-helix bundle structure and do not sterically interfere with the Site 1 and Site 2 binding interfaces. In vitro binding studies demonstrate that somatrogen binds the GHR with affinity comparable to native somatropin, and functional assays in reporter cell lines confirm equivalent maximal activation [14, 18].

4.2 JAK2-STAT5b signaling cascade

Binding of somatrogen to the GHR homodimer produces a conformational change in the receptor intracellular domains that brings the constitutively associated Janus kinase 2 (JAK2) molecules into proximity, permitting transphosphorylation and activation [5, 6]. Activated JAK2 phosphorylates tyrosine residues on the GHR intracellular domain, creating docking sites for SH2-domain-containing signaling proteins, principally STAT5b but also STAT1, STAT3, and the adapter proteins SHC and IRS-1 [5].

Phosphorylated STAT5b dimerizes and translocates to the nucleus, where it binds gamma-interferon-activated sequence (GAS) elements in the promoters of target genes. The principal target gene in hepatocytes is IGF1, encoding insulin-like growth factor 1 (IGF-1), the major mediator of the growth-promoting effects of growth hormone [6]. Additional STAT5b target genes include IGFBP3 (encoding IGF binding protein 3, the principal carrier protein for circulating IGF-1), ALS (acid-labile subunit), and genes involved in hepatic gluconeogenesis and lipolysis.

4.3 IGF-1 axis and growth promotion

The somatrogen-induced increase in circulating IGF-1 drives the principal clinical effect: longitudinal skeletal growth in children with growth hormone deficiency [6]. IGF-1 acts on chondrocytes in the epiphyseal growth plate through the IGF-1 receptor (a receptor tyrosine kinase that activates the PI3K-Akt and RAS-MAPK pathways), stimulating chondrocyte proliferation, hypertrophy, and extracellular matrix synthesis. The combined actions of direct growth hormone signaling on pre-chondrocytes (promoting differentiation and IGF-1 receptor expression) and IGF-1 signaling on proliferating and hypertrophic chondrocytes constitute the dual effector model of growth hormone action on the growth plate [22].

Additional metabolic effects of the GHR signaling cascade include stimulation of protein synthesis (positive nitrogen balance), enhancement of lipolysis (through hormone-sensitive lipase activation and adipocyte triglyceride lipase induction), and modulation of carbohydrate metabolism including transient insulin resistance at the level of the insulin receptor substrate and glucose transporter expression [5, 6].

4.4 Pharmacodynamic profile of somatrogen versus daily somatropin

The once-weekly dosing of somatrogen produces a pharmacodynamic profile that differs from daily somatropin in the temporal pattern of IGF-1 elevation [3, 4]. After subcutaneous injection of somatrogen, serum IGF-1 peaks at approximately day 2, remains elevated through day 4, and returns toward baseline by day 7, producing a peak-to-trough IGF-1 fluctuation that is wider than the relatively steady-state IGF-1 concentrations achieved with daily somatropin [3, 15]. The mean weekly IGF-1 exposure (assessed as time-averaged IGF-1 SDS) is comparable between somatrogen 0.66 mg/kg/week and daily somatropin 0.24 mg/kg/week, consistent with the non-

inferior growth outcomes [7]. The clinical significance of the pulsatile IGF-1 profile relative to the more constant profile of daily dosing is not fully elucidated; preclinical and clinical data have not demonstrated a disadvantage of the pulsatile pattern on growth outcomes through 5 years of follow-up [9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Somatrogon is administered by subcutaneous injection. After a single subcutaneous injection of 15 mg in healthy adult volunteers, peak plasma concentration is reached at approximately 10 hours (range 4 to 16 hours), reflecting the depot absorption kinetics characteristic of subcutaneous protein administration [14]. Absolute bioavailability after subcutaneous injection has not been formally determined but is estimated at approximately 50 to 70 percent based on population pharmacokinetic modeling, consistent with other subcutaneous protein therapeutics [3].

In pediatric patients with growth hormone deficiency receiving the approved dose of 0.66 mg/kg once weekly, somatrogon reaches peak plasma concentration at approximately 12 to 15 hours post-dose, with steady-state conditions achieved by the second or third weekly injection [3, 4].

5.2 Distribution

The volume of distribution of somatrogon after subcutaneous administration is approximately 5 to 7 liters, consistent with distribution predominantly within the vascular and interstitial fluid compartments and limited tissue penetration, as expected for a 40 kDa glycoprotein [3, 14]. There is no accumulation of somatrogon after once-weekly administration, indicating that the 7-day dosing interval exceeds the time required for near-complete elimination from plasma [3].

5.3 Metabolism and elimination

Somatrogon is a protein and is cleared by the catabolic pathways common to endogenous proteins: proteolysis in the liver, kidneys, and reticuloendothelial system [3]. The CTP glycosylation reduces renal clearance by increasing hydrodynamic radius above the glomerular filtration threshold, which is the principal mechanism of half-life extension relative to native growth hormone [1, 2, 18].

The mean terminal elimination half-life is approximately 18.2 hours in healthy adults after a single 15 mg subcutaneous dose [14]. In pediatric patients with growth hormone deficiency receiving repeated weekly doses of 0.66 mg/kg, the mean terminal half-life is approximately 22.4 hours, and the population pharmacokinetic estimated effective half-life (reflecting the functional half-life governing IGF-1 response duration) is approximately 37.7 hours [3, 4]. The discrepancy between the terminal and effective half-lives reflects the contribution of absorption-rate-limited kinetics (flip-flop pharmacokinetics) from the subcutaneous depot.

Apparent clearance in pediatric patients is approximately 0.05 to 0.1 L/h/kg, consistent with protein catabolism rather than hepatic cytochrome P450-mediated metabolism [3]. Somatrogen is not a substrate, inhibitor, or inducer of CYP450 enzymes, though growth hormone treatment may indirectly modulate CYP450 activity (see Section 10).

5.4 Special populations

Pediatric patients: The pharmacokinetics of somatrogen in pediatric patients with growth hormone deficiency have been characterized through population pharmacokinetic analysis of Phase 2 and Phase 3 data. Body weight is the principal covariate affecting exposure, and the weight-based dosing of 0.66 mg/kg normalizes exposure across the pediatric weight range [3].

Adult patients: In adults with growth hormone deficiency, the pharmacokinetic profile is qualitatively similar to the pediatric population, with dose-proportional exposure after subcutaneous injection [21].

Hepatic impairment: Formal pharmacokinetic studies in hepatic impairment have not been conducted. Given that somatrogen is cleared by proteolytic catabolism rather than hepatic CYP metabolism, severe hepatic impairment may modestly alter clearance but the magnitude is not characterized.

Renal impairment: Formal pharmacokinetic studies in renal impairment have not been conducted. The CTP glycosylation reduces renal clearance of the intact molecule; severe renal impairment would be expected to reduce catabolism of circulating proteins but the clinical significance is not characterized.

5.5 Routes of administration

Somatrogon is approved exclusively for subcutaneous injection. The recommended injection sites are the abdomen, thighs, buttocks, or upper arms, with weekly rotation of injection site [17]. Intravenous administration has not been studied and is not recommended. The subcutaneous route produces the depot absorption kinetics that contribute to the extended pharmacodynamic duration.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Somatrogon was characterized in multiple in vitro systems during preclinical development [14, 18]. In cell-based reporter assays using the Ba/F3 cell line stably expressing the human growth hormone receptor and a STAT5-responsive luciferase reporter, somatrogon produced dose-dependent activation with efficacy (maximal response) comparable to native somatropin. The EC₅₀ for GHR activation was modestly higher than native somatropin (approximately 2- to 3-fold), consistent with the steric effects of the CTP domains, but the maximum response was not reduced, indicating full agonist activity [14, 18].

In competitive binding assays using radiolabeled growth hormone and membrane preparations from GHR-expressing cells, somatrogon displaced radiolabeled growth hormone with an IC₅₀ modestly higher than native somatropin, consistent with the cell-based functional data [14].

6.2 In vivo pharmacology: growth promotion

The principal in vivo pharmacology studies were conducted in the hypophysectomized rat model, the classical bioassay for growth hormone activity [14, 18]. Hypophysectomized rats treated with once-weekly somatrogon at total weekly doses equivalent to the total weekly dose of daily somatropin demonstrated comparable tibial growth plate width expansion, comparable body weight gain, and comparable increases in circulating IGF-1. The weekly somatrogon administration produced a pulsatile IGF-1 profile (peak at day 2, trough at day 7) in contrast to the daily fluctuations of daily somatropin, but the integrated IGF-1 exposure and the growth outcomes were equivalent [14].

6.3 In vivo pharmacology: metabolic effects

Preclinical studies in rodent and primate models demonstrated the expected metabolic consequences of growth hormone receptor activation: dose-dependent increases in lean body mass, reductions in adipose tissue mass, transient elevation in

fasting blood glucose, and increases in circulating free fatty acids consistent with enhanced lipolysis [14, 18]. These metabolic effects were qualitatively identical to those of native somatropin and were proportional to the integrated growth hormone receptor activation rather than the peak concentration.

6.4 Toxicology

Preclinical toxicology studies in rats and cynomolgus monkeys established no-observed-adverse-effect levels (NOAELs) that provided adequate safety margins for the clinical doses selected for Phase 1 and Phase 2 evaluation [14]. Repeat-dose toxicology studies of up to 26 weeks duration in monkeys at multiples of the clinical dose did not reveal target organ toxicities beyond the expected pharmacological effects of chronic growth hormone excess (acral enlargement, insulin resistance, soft tissue edema). No genotoxicity, carcinogenicity, or reproductive toxicity signals were identified in the standard preclinical safety battery, consistent with the mechanism of a human protein analog acting through the endogenous growth hormone receptor.

7. Clinical Evidence Base

7.1 Pediatric growth hormone deficiency: pivotal Phase 3 trial

The pivotal global Phase 3 study (NCT02968004; the "OPK trial") was a randomized, open-label, active-controlled, multicenter, non-inferiority trial comparing once-weekly somatrogen (0.66 mg/kg subcutaneously) with once-daily somatropin (Genotropin 0.024 mg/kg/day subcutaneously) in 224 treatment-naïve prepubertal children (Tanner stage I) aged 3 years and older with confirmed growth hormone deficiency (peak stimulated GH less than 10 ng/mL on two provocative tests, height SDS less than negative 2.0, annualized height velocity below the 25th percentile for age and sex) [7].

Patients were randomized 1:1, with stratification by age (3 to less than 6 years, 6 to less than 11 years, 11 years and older), sex, and geographic region. The primary endpoint was annualized height velocity at month 12. The non-inferiority margin was negative 1.8 cm/year for the lower bound of the 95 percent confidence interval of the treatment difference [7].

At month 12, annualized height velocity was 10.12 cm/year (standard deviation 2.85) in the somatrogen arm and 9.78 cm/year (standard deviation 2.66) in the somatropin arm. The treatment difference was 0.33 cm/year (95 percent confidence interval negative 0.38 to 1.05), with the lower bound exceeding the prespecified non-inferiority margin [7]. Non-inferiority was demonstrated. Height velocity at month 6 was 10.60 versus 10.04 cm/year, and change in height SDS from baseline was numerically greater in the somatrogen arm at months 6 and 12 [7].

Mean IGF-1 SDS at month 12 was higher in the somatrogen arm than in the somatropin arm, though IGF-1 SDS values exceeding positive 2.0 were more frequent in the somatrogen arm (approximately 17 percent of somatrogen subjects versus 7 percent of somatropin subjects had at least one IGF-1 SDS value above positive 2.0 during the 12-month period) [7]. Protocol-specified dose reductions were implemented for persistent IGF-1 SDS elevation above positive 2.0.

7.2 Japanese Phase 3 trial

A parallel Phase 3 trial in Japanese children (NCT03874013) randomized 49 treatment-naïve prepubertal children with growth hormone deficiency to once-weekly somatrogen (0.66 mg/kg) or once-daily somatropin (Genotropin 0.025 mg/kg/day) for 12 months [8]. Annualized height velocity at 12 months was 11.0 cm/year in the somatrogen arm versus 10.6 cm/year in the somatropin arm. Non-inferiority was demonstrated, and the safety profile was consistent with the global trial [8].

7.3 Long-term extension data

Following the 12-month randomized period, subjects in both arms of the global Phase 3 trial transitioned to open-label once-weekly somatrogen in an extension study. Data through up to 5 years of somatrogen treatment demonstrated sustained catch-up growth [9]. Mean height SDS increased from baseline by 0.91 at month 12 (end of the randomized period), by 1.47 at extension year 2, and by 1.94 at extension year 4, with continued incremental gains and no plateau, indicating ongoing catch-up toward the normal height range. The safety profile in the extension period was consistent with the randomized period, with no new safety signals identified [9].

7.4 Health-related quality of life

A prespecified analysis of health-related quality of life in the pivotal Phase 3 trial, using the QoLISSY (Quality of Life in Short Stature Youth) instrument, demonstrated improvements in patient-reported and parent-reported quality of life in both treatment arms over 12 months, with no significant difference between somatrogen and daily somatropin [23]. The once-weekly injection frequency did not produce a measurable quality-of-life advantage over daily injection in this analysis, though physician surveys from the Phase 3 trial reported that the majority of treating physicians perceived the once-weekly regimen as offering improved adherence potential [24].

7.5 Adult growth hormone deficiency

A Phase 3 randomized trial of somatrogen in adults with growth hormone deficiency has been completed and reported efficacy in maintaining IGF-1 levels within the normal range and favorable tolerability [21]. The adult indication has not re-

ceived regulatory approval as of the current monograph revision.

8. Sourcing and Quality Verification

Somatrogen is available exclusively as the branded pharmaceutical product Ngenla (Pfizer) in all approved jurisdictions. There is no generic, biosimilar, or research-grade supply of somatrogen at the time of monograph preparation. The compound is a complex glycoprotein produced by recombinant DNA technology in CHO cells, and its manufacture requires specialized cell culture, purification, and formulation capabilities that restrict production to pharmaceutical-grade facilities [19].

Ngenla is supplied as a prefilled pen for subcutaneous injection in two presentations [17]:

- 24 mg/1.2 mL (20 mg/mL) prefilled pen
- 60 mg/1.2 mL (50 mg/mL) prefilled pen

Both presentations are clear to slightly opalescent, colorless to slightly yellow solutions. The formulation contains sodium phosphate, poloxamer 188, phenol (as preservative), and water for injection [17].

Investigators obtaining Ngenla for research purposes should confirm:

- Lot number and expiration date (the product has a 24-month shelf life when stored at 2 to 8 degrees Celsius)
- Visual inspection: solution should be clear to slightly opalescent and free of particulates
- Cold chain integrity: confirm continuous refrigeration at 2 to 8 degrees Celsius from manufacturer to point of use
- Pen functionality: the prefilled pen mechanism should be tested per the instructions for use before administration

Research-grade somatrogen (recombinant CTP-modified growth hormone produced in research-scale CHO cell culture) is not commercially available from standard research chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical). Investigators requiring somatrogen for preclinical research may need to produce the protein in-house from a published or proprietary expression construct, or obtain clinical supplies through Pfizer medical affairs or through a clinical trial supply agreement.

9. Reconstitution and Handling

Somatrogon (Ngenla) is supplied as a ready-to-use prefilled pen and does not require reconstitution [17]. This is a meaningful handling advantage over several other growth hormone products that are supplied as lyophilized powders requiring reconstitution with bacteriostatic water or diluent.

Storage before first use: Refrigerate at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit). Do not freeze. Do not expose to heat. Protect from light in the original carton [17].

Storage after first use: The pen should be returned to the refrigerator after each use and may be stored at 2 to 8 degrees Celsius for up to 28 days after first use [17]. After 28 days, any remaining product should be discarded.

Preparation before injection: Remove the prefilled pen from the refrigerator approximately 30 minutes before injection to allow the solution to reach room temperature. Do not warm by microwave, hot water, or other external heating. Do not shake the pen; shaking may denature the protein. Visually inspect the solution before injection: it should be clear to slightly opalescent and colorless to slightly yellow, without visible particles [17].

Pen priming: New pens must be primed before first use by attaching a new needle and ejecting a small volume of solution until a drop appears at the needle tip [17].

Injection technique: Administer by subcutaneous injection into the abdomen, thighs, buttocks, or upper arms. Rotate the injection site weekly. After injection, hold the pen needle in the skin for at least 10 seconds to ensure complete dose delivery. Remove and safely discard the needle after each injection. Store the pen without the needle attached [17].

Temperature excursions: If the pen has been inadvertently left at room temperature (up to 30 degrees Celsius) for no more than 4 hours, it may be returned to the refrigerator and used within the 28-day after-first-use window. Excursions beyond 4 hours or beyond 30 degrees Celsius require the pen to be discarded [17].

10. Stack Interactions and Combinations

Somatrogon, as a growth hormone receptor agonist, interacts with several drug classes through its pharmacodynamic effects on the IGF-1 axis, carbohydrate metabolism, thyroid hormone metabolism, and cortisol homeostasis. Investigators and clinicians should consider the following interactions:

Glucocorticoids: Growth hormone and cortisol have a bidirectional interaction. Somatrogon treatment may unmask previously undiagnosed central hypoadrenalism by increasing the conversion of cortisone to cortisol through 11-beta-hydroxysteroid dehydrogenase type 1 modulation, and conversely, supraphysiologic glucocorticoid treatment attenuates the growth-promoting effects of somatrogon. Patients with known hypoadrenalism may require increased maintenance or stress doses of glucocorticoid replacement after initiating somatrogon [10, 17].

Thyroid hormone: Growth hormone treatment may unmask central (secondary) hypothyroidism or worsen pre-existing hypothyroidism by increasing peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and by suppressing thyroid-stimulating hormone (TSH) secretion through somatostatin pathway activation. Periodic thyroid function testing is recommended, and thyroid hormone replacement should be initiated or adjusted as indicated [10, 17].

Insulin and oral hypoglycemic agents: Growth hormone is a counter-regulatory hormone that reduces insulin sensitivity by antagonizing insulin signaling at the post-receptor level (inhibition of IRS-1 phosphorylation, induction of SOCS proteins). Patients with pre-existing diabetes mellitus or impaired glucose tolerance may require dose adjustment of insulin or oral hypoglycemic agents after initiating somatrogon [10, 17].

Oral estrogen: Oral estrogen administration (including oral contraceptives and hormone replacement therapy) reduces the hepatic IGF-1 response to growth hormone through first-pass hepatic suppression of GHR expression and STAT5b signaling. Patients receiving concurrent oral estrogen may have an attenuated growth response to somatrogon, and higher doses may be required. Transdermal estrogen does not have this effect [10, 17].

CYP450 substrates: Limited published data indicate that growth hormone treatment increases cytochrome P450-mediated drug clearance. Somatrogon itself is not metabolized by CYP450 enzymes and is not a direct inhibitor or inducer, but the growth hormone receptor signaling may upregulate CYP450 isoforms (notably CYP3A4, CYP2C9, CYP2C19) through indirect transcriptional mechanisms. Drugs metabolized by these isoforms (cyclosporine, sex steroids, anticonvulsants, warfarin) may require monitoring and dose adjustment [17].

Other growth hormone preparations: Concurrent use of somatrogon with daily somatropin or other long-acting growth hormone preparations is pharmacologically redundant and produces additive growth hormone receptor activation with increased risk of dose-dependent adverse effects (insulin resistance, edema, arthralgia). The combination is not recommended.

IGF-1 and IGF-1 analogs: Concurrent use with mecasermin (recombinant IGF-1) or mecasermin rinfabate (IGF-1/IGFBP-3 complex) produces additive IGF-1 receptor activation. The combination has not been studied and is not recommended in clinical practice.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at the approved pediatric dose (0.66 mg/kg once weekly) in the pivotal Phase 3 trial were [7, 10]:

- Injection site pain (39.4 percent somatrogon versus 25.2 percent somatropin)
- Injection site erythema (8.3 percent somatrogon versus 0 percent somatropin)
- Injection site pruritus (3.7 percent somatrogon versus 0 percent somatropin)
- Nasopharyngitis (21.1 percent somatrogon versus 23.5 percent somatropin)
- Headache (11.0 percent somatrogon versus 13.0 percent somatropin)
- Pyrexia (11.0 percent somatrogon versus 8.7 percent somatropin)
- Anemia (6.4 percent somatrogon versus 5.2 percent somatropin)
- Cough (6.4 percent somatrogon versus 6.1 percent somatropin)
- Vomiting (6.4 percent somatrogon versus 4.3 percent somatropin)
- Hypothyroidism (5.5 percent somatrogon versus 2.6 percent somatropin)

The majority of adverse events were mild to moderate in severity (somatrogon 78.9 percent, somatropin 79.1 percent). No treatment-related deaths occurred in the clinical program [7, 10].

11.2 Growth hormone class effects

The following growth hormone class-effect adverse events were observed at rates consistent with daily somatropin [10, 17]:

- Transient hyperglycemia and impaired glucose tolerance, reflecting the counter-regulatory metabolic effects of growth hormone receptor activation
- Benign intracranial hypertension (pseudotumor cerebri), rare, presenting with headache, visual changes, and papilledema; requires prompt ophthalmologic evaluation and consideration of treatment discontinuation
- Slipped capital femoral epiphysis, associated with rapid growth and the biomechanical stresses on the epiphysis during growth hormone treatment

- Progression of pre-existing scoliosis during rapid growth
- Fluid retention and peripheral edema (more common in adults than in the pediatric population studied)
- Pancreatitis (rare; observed in postmarketing surveillance of the growth hormone class)

11.3 Immunogenicity

Immunogenicity of somatrogen is the most notable safety finding distinguishing it from native somatropin [7, 11]. In the pivotal Phase 3 trial, 84 of 109 somatrogen-treated subjects (77.1 percent) tested positive for anti-drug antibodies (ADAs) at any time during the 12-month study period, compared with 18 of 115 somatropin-treated subjects (15.6 percent). The higher ADA incidence with somatrogen is attributable to the novel CTP-hGH fusion protein epitopes that are not present in native somatropin [11].

Critically, no neutralizing antibodies (antibodies that interfere with somatrogen binding to the growth hormone receptor) were detected in any somatrogen-treated subject [7, 11]. The ADAs were predominantly low-titer, non-neutralizing IgG antibodies directed against the CTP domains rather than the growth hormone moiety. No clinically significant impact of ADA status on efficacy (height velocity, height SDS change, IGF-1 response) or safety was observed during the 12-month randomized period or during the subsequent 30-month open-label extension period [7, 9, 11].

The immunogenicity data should be interpreted in the context of the assay methodology: anti-drug antibody testing is highly sensitive and assay-dependent, and cross-study comparison of ADA incidence rates is not reliable. The clinical significance of the observed ADAs is assessed by their impact on pharmacokinetics, pharmacodynamics, efficacy, and safety rather than by the incidence rate alone [11].

11.4 Contraindications

Somatrogen is contraindicated in patients with active malignancy, acute critical illness, active proliferative or severe non-proliferative diabetic retinopathy, and known hypersensitivity to somatrogen or any excipient. Somatrogen should not be used after closure of the epiphyses in the pediatric growth indication [17].

11.5 Pregnancy and lactation

There are no adequate data on the use of somatrogen in pregnant women. Animal reproduction studies have not been conducted with somatrogen. The potential risk to the fetus is unknown. Growth hormone treatment is generally discontinued during pregnancy. There are no data on the presence of somatrogen in human milk or on the effects on the breastfed infant [17].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five growth hormone and growth-promoting preparations against somatrogon, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal growth hormone preparations with substantive clinical evidence in pediatric growth hormone deficiency, with priority on those with once-weekly dosing that share somatrogon's clinical positioning.

12.1 Somapacitan (Sogroya; Novo Nordisk)

Mechanism: Somapacitan is a long-acting growth hormone derivative consisting of human growth hormone with a single amino acid substitution (Leu101Cys) and a covalent albumin-binding moiety (a C18 fatty acid chain attached to the Cys101 position via a linker) [25]. The albumin binding extends the circulating half-life to approximately 30 to 35 hours by shielding the molecule from renal clearance and proteolytic degradation while in the albumin-bound state. Somapacitan is a permanently modified GH derivative that releases growth hormone activity through reversible albumin binding.

Development trajectory: Novo Nordisk advanced somapacitan through Phase 3 clinical trials in both pediatric and adult growth hormone deficiency. The REAL4 Phase 3 trial in 200 treatment-naïve children with GHD demonstrated non-inferiority of once-weekly somapacitan (0.16 mg/kg) to once-daily somatropin (Norditropin) on annualized height velocity at 52 weeks [26]. Somapacitan was approved by the FDA for adult growth hormone deficiency (Sogroya) in 2020 and for pediatric GHD in 2024.

Novelty: Moderate. The albumin-binding fatty acid technology is well established in Novo Nordisk's platform (semaglutide, insulin degludec, insulin detemir) but is a novel application to growth hormone.

Effect size: The REAL4 trial reported annualized height velocity of 10.0 cm/year for somapacitan versus 9.8 cm/year for daily somatropin at 52 weeks, comparable to the somatrogen Phase 3 results [26]. A network meta-analysis reported no statistically significant difference in annualized height velocity between somapacitan and somatrogen [27].

Promising potential: High. Somapacitan has achieved regulatory approval for both pediatric and adult GHD indications and is actively marketed as a once-weekly alternative to daily somatropin.

Side-effect profile: The principal adverse events are injection site reactions, headache, and arthralgia. ADA incidence is lower than somatrogen. The albumin-binding mechanism avoids the novel fusion protein epitopes that drive the somatrogen ADA signal [25, 26].

Overall validation: High. Two approved indications, robust Phase 3 data, and an established commercial presence.

Comparison to somatrogen: Somapacitan and somatrogen are directly competitive as once-weekly growth hormone preparations for pediatric GHD. Somapacitan has the advantage of lower immunogenicity and a second approved indication (adult GHD). Somatrogen has the advantage of preserving the unmodified growth hormone amino acid sequence (the CTP modification is appended rather than substitutive) and numerically higher growth velocity in cross-trial comparison, though the difference is not statistically significant in network meta-analysis.

12.2 Lona pegsomatropin (Skytrofa; Ascendis Pharma)

Mechanism: Lona pegsomatropin is a prodrug consisting of native somatropin covalently conjugated to a methoxy-polyethylene glycol (mPEG) carrier through a proprietary TransCon (transient conjugation) linker that hydrolyzes slowly under physiological conditions, releasing unmodified somatropin over approximately 7 days [28]. The prodrug approach delivers native growth hormone rather than a permanently modified derivative.

Development trajectory: The heiGHt Phase 3 trial randomized 161 treatment-naïve children with GHD to once-weekly lona pegsomatropin (0.24 mg/kg/week expressed as somatropin equivalent) or once-daily somatropin (Genotropin 0.024 mg/kg/day) and demonstrated superiority of lona pegsomatropin on annualized

height velocity at 52 weeks (11.2 cm/year versus 10.3 cm/year) [28, 29]. Lonapegsomatropin was approved by the FDA in August 2021 and by the EMA in 2022.

Novelty: High. The TransCon prodrug technology is a mechanistically distinct approach to half-life extension that releases unmodified growth hormone, preserving the endogenous pharmacology entirely.

Effect size: The heiGHt trial demonstrated superiority (not merely non-inferiority) over daily somatropin, with a treatment difference of approximately 0.9 cm/year. A network meta-analysis reported statistically significantly higher annualized height velocity for lonapegsomatropin than for somatrogen and somapacitan [27].

Promising potential: High. First-to-market among the once-weekly long-acting growth hormones with FDA approval, superiority data, and an expanding label.

Side-effect profile: The principal adverse events are injection site reactions, headache, pyrexia, and nasopharyngitis. ADA incidence is low, as the compound releases unmodified somatropin. No novel safety signals have been identified [28, 29].

Overall validation: High. Superiority data, regulatory approval, and growing clinical experience.

Comparison to somatrogen: Lonapegsomatropin has the clinical advantage of superiority data over daily somatropin (versus non-inferiority for somatrogen), lower immunogenicity (release of unmodified GH), and earlier FDA approval. Somatrogen has the advantage of simpler molecule design (fusion protein versus PEG prodrug, avoiding the theoretical concerns about PEG accumulation that have been discussed in the literature) and a ready-to-use prefilled pen presentation.

12.3 Daily somatropin (Genotropin, Norditropin, Humatrope, Nutropin, Saizen)

Mechanism: Recombinant human growth hormone (191-amino-acid protein identical to native pituitary growth hormone), produced in *E. coli* (Genotropin, Humatrope) or mammalian cell lines, administered as a daily subcutaneous injection [30]. The mechanism of action is identical to somatrogen but without half-life extension, requiring daily injection to maintain physiological IGF-1 levels.

Development trajectory: Daily somatropin has been available since 1985 (when recombinant somatropin replaced pituitary-extracted growth hormone following the Creutzfeldt-Jakob disease contamination crisis) and is the established standard of care with decades of clinical experience across multiple approved indications (pediatric GHD, adult GHD, Turner syndrome, small for gestational age, Prader-Willi syndrome, chronic renal insufficiency, idiopathic short stature) [30].

Novelty: None. Daily somatropin is the reference standard against which all novel growth hormone preparations are evaluated.

Effect size: In the somatrogon Phase 3 trial, daily somatropin (Genotropin 0.024 mg/kg/day) produced annualized height velocity of 9.78 cm/year at 12 months, consistent with the established efficacy of daily growth hormone replacement [7].

Promising potential: Stable. Daily somatropin will remain available as a lower-cost alternative, particularly in markets where long-acting preparations are not reimbursed or where patient or physician preference favors daily dosing.

Side-effect profile: Decades of postmarketing surveillance have established the safety profile: injection site reactions, headache, peripheral edema, arthralgia, and the growth hormone class effects described in Section 11.2. The long-term safety record is extensive and provides the reference against which novel preparations are compared [30].

Overall validation: Very high. The most extensively validated growth hormone preparation with the longest clinical track record.

Comparison to somatrogon: Daily somatropin is the active comparator in the somatrogon Phase 3 trial. Somatrogon offers the advantage of reduced injection frequency (once weekly versus daily, reducing from 365 to 52 injections per year). Daily somatropin has the advantages of lower cost, extensive long-term safety data, multiple approved indications, and familiarity for patients and clinicians. The growth efficacy is equivalent based on the non-inferiority data.

12.4 Somatorelin (GHRH 1-29; Geref)

Mechanism: Somatorelin is the 29-amino-acid N-terminal fragment of growth hormone-releasing hormone (GHRH) that stimulates endogenous growth hormone secretion from anterior pituitary somatotroph cells through the GHRH receptor, a G-protein-coupled receptor that activates the cAMP-PKA signaling cascade [31].

Unlike somatogon and the other direct growth hormone preparations, somatorelin acts upstream of growth hormone secretion and requires intact pituitary somatotroph function.

Development trajectory: Somatorelin was approved by the FDA in 1997 (Geref Diagnostic, Serono) as a diagnostic agent for the evaluation of growth hormone secretory capacity and was subsequently withdrawn from the US market. It has been used in research settings and in compounding pharmacy contexts as a growth hormone secretagogue, though not as a registered therapeutic for growth hormone deficiency [31].

Novelty: Low. The compound is a native hormone fragment with well-characterized pharmacology and limited therapeutic novelty.

Effect size: In diagnostic applications, somatorelin produces a growth hormone secretory response that is used to assess pituitary reserve. As a therapeutic agent for growth hormone deficiency, somatorelin is limited by the requirement for intact pituitary function: patients with organic growth hormone deficiency (pituitary destruction, irradiation, congenital hypopituitarism) do not respond. Effect size in growth promotion in responders is not established in registration-quality clinical trials.

Promising potential: Low. The compound is no longer marketed, has limited therapeutic applicability (requires intact pituitary), and has been superseded by direct growth hormone preparations.

Side-effect profile: The principal adverse events are injection site reactions, facial flushing, and transient nausea. The safety profile reflects the physiological growth hormone secretory response and is generally benign [31].

Overall validation: Low. Validated as a diagnostic agent but not as a therapeutic growth hormone replacement.

Comparison to somatogon: Somatorelin acts through an entirely different mechanism (pituitary stimulation versus direct GHR agonism) and is not a direct therapeutic alternative to somatogon. The comparison illustrates the distinction between growth hormone secretagogues and growth hormone replacements: somatogon provides direct, dose-controllable, pituitary-independent growth hormone receptor activation, while somatorelin depends on residual pituitary function and produces a variable, physiologically modulated response.

12.5 Tesamorelin (Theratechnologies; Egrifta)

Mechanism: Tesamorelin is a synthetic analog of growth hormone-releasing hormone (GHRH 1-44) with a trans-3-hexenoic acid modification at the N-terminus that confers resistance to dipeptidyl peptidase IV cleavage, extending the circulating half-life beyond the minutes of native GHRH to approximately 26 minutes [32]. Like somatostatin, tesamorelin acts as a GHRH receptor agonist on pituitary somatotroph cells and requires intact pituitary function. Tesamorelin is approved for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy, not for growth hormone deficiency [32].

Development trajectory: Theratechnologies developed tesamorelin through Phase 3 clinical trials in HIV-associated lipodystrophy. Two pivotal trials demonstrated significant reduction in visceral adipose tissue (approximately 15 to 18 percent reduction versus placebo) at a dose of 2 mg daily subcutaneously [32]. The FDA approved tesamorelin (Egrifta) in November 2010.

Novelty: Moderate. The DPP-IV-resistant GHRH analog concept is a meaningful advance over native GHRH for the lipodystrophy indication.

Effect size: Significant in the approved indication (visceral fat reduction). Not evaluated in growth promotion in pediatric GHD.

Promising potential: Moderate in the lipodystrophy indication. Not relevant as a pediatric GHD therapeutic.

Side-effect profile: The principal adverse events are injection site reactions (erythema, pruritus), arthralgia, peripheral edema, and the transient hyperglycemia expected from growth hormone axis stimulation [32].

Overall validation: Moderate. Validated for the lipodystrophy indication but not for growth hormone deficiency.

Comparison to somatostatin: Tesamorelin is not a direct therapeutic alternative to somatostatin for pediatric growth hormone deficiency. The comparison illustrates the distinction between GHRH agonists (indirect growth hormone axis stimulation, pituitary-dependent, approved for a metabolic rather than growth indication) and direct growth hormone receptor agonists (somatostatin, direct, pituitary-independent, approved for growth hormone deficiency). Somatostatin is the appropriate

choice for growth hormone deficiency; tesamorelin addresses a different clinical need (visceral adiposity reduction in HIV lipodystrophy) through an overlapping but distinct pharmacological pathway.

12.6 Comparator summary

The five comparators occupy distinct positions in the growth hormone pharmacology landscape. **Somapacitan** is the most directly competitive preparation, sharing the once-weekly dosing frequency, comparable efficacy, and the permanently modified derivative approach, with the advantages of lower immunogenicity and dual-indication approval. **Lona pegsomatropin** has the strongest efficacy signal (superiority data) and the mechanistic advantage of releasing unmodified growth hormone, with early market presence. **Daily somatropin** remains the reference standard with the deepest safety database and the broadest indication set, offset by the burden of daily injection. **Somatorelin** and **tesamorelin** illustrate the upstream GHRH-agonist approach that is mechanistically distinct from direct growth hormone receptor agonism and is not applicable to most patients with growth hormone deficiency.

Somatrogon occupies a defined position in this landscape as a once-weekly long-acting growth hormone receptor agonist with Phase 3 non-inferiority data, regulatory approval in major jurisdictions, a prefilled pen presentation requiring no reconstitution, and the CTP-based half-life extension platform that preserves the native growth hormone sequence. Its principal differentiators are the CTP technology (no PEGylation, no albumin binding, no chemical conjugation), the ready-to-use formulation, and the extensive Phase 3 and long-term extension dataset. Its principal limitation relative to the comparators is the higher immunogenicity (77 percent ADA incidence, though without neutralizing activity or clinical impact), the non-inferiority rather than superiority efficacy outcome, and the later market entry relative to lona pegsomatropin.

The clinical choice among the once-weekly long-acting growth hormones (somatrogon, somapacitan, lona pegsomatropin) is determined by prescriber and patient preference, reimbursement status, formulation convenience, and institutional experience rather than by clear efficacy or safety superiority of any single agent. All three preparations have demonstrated non-inferiority or superiority to daily soma-

tropin with acceptable safety profiles and represent a meaningful advance in the management of pediatric growth hormone deficiency through reduction of injection burden.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Somatrogen is approved by the United States Food and Drug Administration and by multiple international regulatory agencies for the treatment of pediatric growth hormone deficiency. Investigators should consult their local regulatory authority and the current prescribing information before any clinical or research application.