

RESEARCH MONOGRAPH . COMPOUND PROFILE

Mecasermin

A recombinant analog of endogenous insulin-like growth factor 1 developed at Genentech and commercialized by Tercica (later Ipsen) for the treatment of severe primary IGF-1 deficiency, distinguished from growth hormone replacement by its direct activation of the type 1 IGF-1 receptor and its investigational applications in neuroprotection, neurodevelopmental disorders, and metabolic disease.

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ABSTRACT

Mecasermin is recombinant human insulin-like growth factor 1 (rhIGF-1), a 70-amino-acid, 7649-dalton non-glycosylated polypeptide produced in *Escherichia coli* by recombinant DNA technology. The amino acid sequence of mecasermin is identical to that of endogenous human IGF-1, a peptide hormone synthesized principally in the liver under the transcriptional control of growth hormone and serving as the primary mediator of postnatal somatic growth, skeletal maturation, and metabolic homeostasis.

Mecasermin is the active pharmaceutical ingredient in Increlex (Ipsen), the only therapy approved by the United States Food and Drug Administration (August 2005, priority review) and by the European Medicines Agency (2007) for the long-term treatment of growth failure in pediatric patients with severe primary insulin-like growth factor 1 deficiency (SPIGFD), a condition most classically represented by Laron syndrome (growth hormone receptor deficiency) and by growth hormone gene deletion with neutralizing antibodies to exogenous growth hormone.

The mechanism of action is direct agonism of the type 1 IGF-1 receptor (IGF-1R), a transmembrane receptor tyrosine kinase structurally homologous to the insulin receptor. Ligand binding activates autophosphorylation of the intracellular kinase domain and recruitment of insulin receptor substrate (IRS) adapter proteins, leading to bifurcated downstream signaling through the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway (metabolic, anti-apoptotic, and translational outcomes) and the Ras/Raf/mitogen-activated protein kinase (MAPK/ERK) pathway (mitogenic, proliferative, and differentiative outcomes). In the growth plate, IGF-1R activation stimulates chondrocyte proliferation and hypertrophy in the proliferative and hypertrophic zones of the epiphyseal cartilage, driving longitudinal bone growth through endochondral ossification. The metabolic actions include stimulation of glucose

uptake, amino acid incorporation into protein, fatty acid uptake, and suppression of hepatic glucose output, producing a composite anabolic and mildly hypoglycemic pharmacology.

Pharmacokinetics following subcutaneous injection are characterized by near-complete bioavailability, a time to peak plasma concentration of approximately 2 hours, and a terminal elimination half-life that is critically dependent on circulating levels of IGF-binding protein 3 (IGFBP-3) and the acid-labile subunit (ALS). In patients with severe primary IGF-1 deficiency, who characteristically have low IGFBP-3 and ALS concentrations, the terminal half-life is approximately 5.8 hours; in healthy individuals with normal binding protein levels, the half-life extends to approximately 19 hours owing to sequestration in the 150-kilodalton ternary complex of IGF-1, IGFBP-3, and ALS. The volume of distribution is approximately 0.257 liters per kilogram. Clearance is inversely proportional to IGFBP-3 concentration and is estimated at 0.04 liters per hour per kilogram at an IGFBP-3 level of 3 micrograms per milliliter. Metabolism is predominantly lysosomal, principally in the liver and kidneys, with degradation to amino acids; less than 0.1 percent of administered drug is excreted unchanged in urine.

The pivotal clinical evidence base consists of five open-label, single-arm studies in 71 pediatric patients with SPIGFD treated for a mean duration of 3.9 years (274 subject-years of exposure). First-year height velocity increased from a baseline of 2.6 centimeters per year to 8.0 centimeters per year (p less than 0.0001), with sustained growth acceleration over 8 or more years of continuous treatment. The principal adverse event is hypoglycemia, reported in 42 percent of subjects; severe hypoglycemia requiring assistance occurred in 5 subjects, and hypoglycemic seizures or loss of consciousness occurred in 4 subjects. Hypoglycemia is mitigated by administration within 20 minutes of a meal or snack. Other notable adverse events include tonsillar and adenoidal hypertrophy (15 percent), injection site lipohypertrophy, and intracranial hypertension with papilledema (3 subjects). Long-term safety monitoring has not identified an increased incidence of malignancy

at approved doses. Investigational applications of mecasermin extend to Rett syndrome (Phase 1, with improvement in apnea and neurobehavioral parameters), amyotrophic lateral sclerosis (negative in controlled trials), and various neuroprotective contexts supported by the neurotrophic properties of IGF-1.

This monograph reviews the chemistry and recombinant production of mecasermin; the IGF-1R signaling pharmacology in molecular detail; the comprehensive pharmacokinetic record including binding protein dependence; the clinical evidence base across growth failure, neuroprotection, and metabolic indications; sourcing and quality verification for research-grade material; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five alternative growth-promoting or IGF-1-axis compounds against mecasermin on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Mecasermin.

Marketed name: Increlex (Ipsen; United States, European Union, and additional jurisdictions). The product was originally marketed by Tercica, Inc., which was acquired by Ipsen in 2008.

Development codes: The compound does not carry a conventional small-molecule development code. The recombinant protein was developed at Genentech, Inc. under the designation recombinant human insulin-like growth factor 1 (rhIGF-1). Tercica acquired exclusive rights to develop, commercialize, and manufacture the product from Genentech and advanced it through the regulatory pathway as Increlex [1].

Chemical Abstracts Service registry number: 68562-41-4 (mecasermin, recombinant human IGF-1).

UniProt accession: P05019 (human insulin-like growth factor I precursor; the mature 70-amino-acid form corresponds to residues 49 to 118 of the precursor polypeptide).

DrugBank identifier: DB01277.

International Union of Pure and Applied Chemistry name: Not applicable (biological macromolecule). The compound is designated by its International Nonproprietary Name (mecasermin) and by the descriptor "recombinant human insulin-like growth factor 1."

1.2 Structural class and chemistry

Mecasermin is a recombinant protein identical in primary amino acid sequence to endogenous human insulin-like growth factor 1 (IGF-1). The structural class is a single-chain polypeptide hormone of the insulin superfamily, sharing approximately 50 percent sequence homology with proinsulin [2].

Amino acid sequence: The mature protein consists of 70 amino acids arranged in four domains (B, C, A, and D, numbered by analogy to the insulin domains). The sequence is: GPETLCGAELVDALQFVCGDRGFYFNKPTGYGSSRRAPQTGIVDECCFRSCDLRRLEMYCAPLKPAKSA. Three intramolecular disulfide bonds (Cys6-Cys48, Cys18-Cys61, Cys47-Cys52) stabilize the tertiary structure [2, 3].

Molecular weight: 7649 daltons (monoisotopic mass of the mature polypeptide).

Physical properties: The recombinant protein is a non-glycosylated, single-chain polypeptide produced in *Escherichia coli*. The commercial formulation (Increlex) is a sterile, aqueous, clear, and colorless solution at pH approximately 5.4, containing 10 mg/mL mecasermin with benzyl al-

cohol (9 mg/mL) as preservative, polysorbate 20 (2 mg/mL) as surfactant, glacial acetic acid, sodium acetate, and sodium chloride [4].

Structural homology: IGF-1 is structurally homologous to IGF-2 (approximately 62 percent sequence identity) and to proinsulin (approximately 50 percent). The three-dimensional structure, determined by nuclear magnetic resonance spectroscopy, consists of three alpha-helices connected by loops, with the disulfide bonds maintaining the characteristic insulin-fold tertiary structure [2].

1.3 Recombinant production

Mecasermin is produced by recombinant DNA technology in *Escherichia coli* modified by insertion of the gene encoding the mature human IGF-1 polypeptide. The recombinant protein is expressed as inclusion bodies, solubilized under denaturing conditions, refolded to the native three-disulfide-bond conformation, and purified by multiple chromatographic steps (typically ion exchange, hydrophobic interaction, and size exclusion chromatography) [5]. The refolding step is critical for production yield, as incorrect disulfide bond pairing produces inactive or partially active isoforms. Industrial processes have been optimized to achieve greater than 95 percent correct disulfide pairing, and the final product is characterized by reversed-phase high-performance liquid chromatography, size-exclusion chromatography, peptide mapping, mass spectrometry, and bioassay (typically a cell-based IGF-1R phosphorylation or proliferation assay) [5, 6]. The *E. coli* expression system does not produce glycosylated product; endogenous human IGF-1 is also non-glycosylated, so the recombinant product is structurally identical to the natural hormone.

2. Abstract

Mecasermin (recombinant human insulin-like growth factor 1, rhIGF-1) is a 70-amino-acid polypeptide hormone of the insulin superfamily, produced by recombinant DNA technology in *Escherichia coli*, that is identical in amino acid sequence to endogenous human IGF-1. The compound is the active pharmaceutical ingredient in Increlex (Ipsen), the only therapy approved by the United States Food and Drug Administration (August 30, 2005) and by the European Medicines Agency (2007) for the long-term treatment of growth failure in pediatric patients with severe primary insulin-like growth factor 1 deficiency (SPIGFD) [1, 4].

Endogenous IGF-1 is the principal mediator of the growth-promoting effects of growth hormone (GH). Under physiological conditions, GH binds its hepatic receptor and stimulates transcription and secretion of IGF-1, which then acts in an endocrine, paracrine, and autocrine manner on the type 1 IGF-1 receptor (IGF-1R) to drive longitudinal bone growth, soft tissue anabolism, and metabolic regulation. In patients with SPIGFD, the GH-IGF-1 axis is disrupted at or below the level of the GH receptor: circulating GH levels are normal or elevated, but IGF-1 production is deficient. The prototypic form of SPIGFD is Laron syndrome, first described by Zvi Laron in 1966 in children of Yemenite Jewish origin who presented with clinical features of GH deficiency but paradoxically elevated serum GH concentrations [7, 8]. The molecular basis was elucidated in 1987 with the cloning of the GH receptor gene and the identification of loss-of-function mutations in affected kindreds.

These patients are unresponsive to exogenous GH replacement. The therapeutic rationale for mecasermin is therefore replacement of the deficient downstream effector, IGF-1, by direct subcutaneous administration, bypassing the defective GH receptor. At approved doses (0.04 to 0.12 mg/kg twice daily by subcutaneous injection), mecasermin produces a first-year height velocity of approximately 8.0 centimeters per year compared to a pre-treatment baseline of approximately 2.6 centimeters per year in children with SPIGFD, with sustained growth acceleration over multi-year treatment [1, 9].

The principal safety concern is hypoglycemia, reflecting the insulin-like metabolic activity of IGF-1. The compound stimulates peripheral glucose uptake and suppresses hepatic glucose output, and these effects are most pronounced in the first hours after injection in the fasting or post-absorptive state. Administration with a meal or snack substantially mitigates hypoglycemic risk [4]. Other adverse events include lymphoid tissue hypertrophy (tonsillar and adenoidal enlargement), injection site lipohypertrophy, and rare intracranial hypertension.

Investigational applications extend beyond the approved pediatric growth indication. A Phase 1 trial in Rett syndrome (Khwaja et al. 2014) demonstrated safety and tolerability with preliminary signals of improvement in apnea and neurobehavioral parameters [10]. Trials in amyotrophic lateral sclerosis have not demonstrated efficacy [11]. The neurotrophic and neuroprotective properties of IGF-1 continue to support investigation in neurological and neurodevelopmental disorders.

This monograph documents the chemistry, recombinant production, and structural characterization of mecasermin; the IGF-1R signaling pharmacology; the pharmacokinetic profile including binding protein dependence; the clinical evidence base across growth failure and investigational indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a structured comparative assessment of five alternative growth-axis compounds against mecasermin on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin of the IGF-1 concept

The existence of a serum factor mediating the growth-promoting activity of growth hormone was proposed by Salmon and Daughaday in 1957, who demonstrated that serum from GH-treated hypophysectomized rats stimulated sulfate incorporation into cartilage in vitro, whereas GH itself did not [12]. The factor was initially termed "sulfation factor" and subsequently "somatomedin." Rinderknecht and Humbel purified and sequenced the two principal somatomedins from human serum in 1978, designating them insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) on the basis of their structural homology to proinsulin [2].

3.2 Discovery of Laron syndrome

Zvi Laron, working at the Tel Aviv Medical Center, began clinical investigations in 1958 of dwarfed children, principally recent immigrants from Yemen and the Middle East, who presented with clinical features of isolated growth hormone deficiency but, paradoxically, had elevated serum immunoreactive GH concentrations. In 1966, Laron, Pertzelan, and Mannheimer published the first formal description of this syndrome, which became known as Laron-type dwarfism or growth hormone insensitivity syndrome [7]. The molecular basis was established in 1989 when Godowski et al. identified mutations in the GH receptor gene in affected patients, confirming that the syndrome resulted from end-organ resistance to GH rather than from GH deficiency [8]. The Ecuadorian cohort of approximately 100 individuals with GH receptor deficiency, studied by Guevara-Aguirre and colleagues since 1987, has provided extensive longitudinal natural history and treatment data and the remarkable observation of near-complete absence of cancer and diabetes in affected individuals over 25 years of follow-up [13].

3.3 Recombinant IGF-1 production and early clinical trials

With the biosynthesis of recombinant human IGF-1 achieved in the mid-1980s using *E. coli* expression systems, therapeutic trials became feasible. Genentech produced the initial clinical-grade material. Open-label treatment studies in patients with Laron syndrome and other forms of severe primary IGF-1 deficiency were initiated in the early 1990s by multiple groups, including Laron in Israel, Guevara-Aguirre in Ecuador, Savage in the United Kingdom, and Backeljauw and Underwood in the United States [9, 14]. These studies demonstrated significant acceleration of linear growth velocity, with first-year height velocities of 6 to 9 centimeters per year compared to untreated baselines of 2 to 4 centimeters per year.

3.4 Regulatory approval and commercialization

Tercica, Inc. acquired exclusive rights to develop, commercialize, and manufacture mecasermin from Genentech. The company submitted a Biologics License Application (BLA) to the FDA, which was granted priority review. On August 30, 2005, the FDA approved Increlex (mecasermin injection) for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency [1]. The approval was based on five clinical trials in 71 pediatric patients representing 274 subject-years of exposure. The European Medicines Agency approved Increlex in 2007. Ipsen acquired Tercica in 2008 and has marketed the product since that date.

3.5 Mecasermin rinfabate (IPLEX)

A related product, mecasermin rinfabate (IPLEX, Insmed Incorporated), consisted of recombinant human IGF-1 complexed with recombinant human IGFBP-3, designed to mimic the physiological binary complex and extend the circulating half-life of IGF-1 while reducing the incidence of free-IGF-1-related hypoglycemia. IPLEX received FDA approval in December 2005 for the same SPIGFD indication. However, in March 2007, following a patent infringement settlement between Insmed, Tercica, and Genentech, Insmed agreed to cease marketing IPLEX in the United States for growth-related indications [15]. The European marketing authorization application was withdrawn. IPLEX is no longer commercially available for growth failure. Insmed retained rights to develop the complex for other therapeutic indications (HIV-associated adipose redistribution syndrome, myotonic muscular dystrophy) but has not brought the product to market for any indication [15].

3.6 Investigational expansion

Following regulatory approval for SPIGFD, mecasermin has been investigated in several additional indications. The FDA has granted orphan drug designations for mecasermin in Rett syndrome, Fragile X syndrome, and SHANK3 gene deficiency syndrome. A Phase 1 trial in Rett syndrome (Khwaja et al. 2014, Boston Children's Hospital) demonstrated safety and preliminary efficacy signals [10]. Trials in amyotrophic lateral sclerosis using subcutaneous rhIGF-1 have been conducted but have not demonstrated significant clinical benefit [11]. The investigational trajectory of mecasermin remains active in neurodevelopmental and neuroprotective contexts.

4. Mechanism of Action

Mecasermin exerts its biological effects through direct activation of the type 1 insulin-like growth factor receptor (IGF-1R), a transmembrane receptor tyrosine kinase of the insulin receptor family. The downstream signaling produces growth-promoting, anabolic, metabolic, and cytoprotective effects across multiple tissue types.

4.1 IGF-1 receptor binding and activation

The IGF-1R is a heterotetrameric transmembrane glycoprotein composed of two extracellular alpha subunits and two transmembrane beta subunits linked by disulfide bonds, structurally homologous to the insulin receptor (approximately 60 percent sequence identity in the kinase domain) [16]. IGF-1 binds to the alpha subunits at the ligand-binding domain with a dissociation constant of approximately 1 nanomolar, approximately 100-fold higher affinity than insulin for the same receptor. Binding induces a conformational change that activates the intrinsic tyrosine kinase activity of the beta subunits, resulting in trans-autophosphorylation of tyrosine residues in the activation loop (Tyr1131, Tyr1135, Tyr1136), in the juxtamembrane domain (Tyr950), and in the C-terminal tail [16, 17].

Phosphorylation of Tyr950 creates a docking site for the insulin receptor substrate (IRS) family of adapter proteins (IRS-1, IRS-2, IRS-3, IRS-4) and for Shc (Src homology collagen) proteins, which initiate the two principal downstream signaling cascades [17].

4.2 PI3K/Akt/mTOR pathway

IRS-1 and IRS-2 recruit and activate class IA phosphatidylinositol 3-kinase (PI3K), which phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 recruits the serine/threonine kinase Akt (protein kinase B) to the plasma membrane, where it is phosphorylated and activated by phosphoinositide-dependent kinase 1 (PDK1) and by the mechanistic target of rapamycin complex 2 (mTORC2) [17, 18].

Activated Akt phosphorylates multiple downstream substrates, producing the following functional consequences relevant to the growth and metabolic pharmacology of mecasermin:

- **Glucose metabolism:** Akt promotes translocation of GLUT4 glucose transporters to the plasma membrane in skeletal muscle and adipose tissue, stimulating glucose uptake. Akt also phosphorylates and inactivates glycogen synthase kinase 3 (GSK3), promoting glycogen synthesis, and suppresses hepatic gluconeogenesis through phosphorylation of the forkhead box protein O1 (FOXO1) transcription factor [18]. These actions account for the insulin-like hypoglycemic activity of mecasermin.
- **Protein synthesis and cell growth:** Akt activates mTOR complex 1 (mTORC1) through phosphorylation and inhibition of the tuberous sclerosis complex (TSC1/TSC2). mTORC1 phosphorylates ribosomal protein S6 kinase (S6K1) and eukaryotic initiation factor 4E-binding

protein 1 (4E-BP1), promoting cap-dependent mRNA translation and ribosome biogenesis [18].

- **Anti-apoptosis:** Akt phosphorylates and inactivates the pro-apoptotic protein BAD and the forkhead transcription factors FOXO1 and FOXO3a, promoting cell survival. This anti-apoptotic activity is the molecular basis for the cytoprotective and neurotrophic properties of IGF-1 [19].

4.3 Ras/MAPK/ERK pathway

Phosphorylated Shc recruits the Grb2-SOS complex, activating the small GTPase Ras. Ras initiates the canonical mitogen-activated protein kinase (MAPK) cascade: Raf (MAPKKK), MEK1/2 (MAPKK), and ERK1/2 (MAPK). Activated ERK1/2 translocates to the nucleus and phosphorylates transcription factors (Elk-1, c-Fos, c-Myc) that drive cell proliferation, differentiation, and gene expression programs [17, 20]. In chondrocytes of the growth plate, the MAPK/ERK pathway is the principal mitogenic signal driving proliferative zone expansion and the transition to the hypertrophic zone of endochondral ossification [20, 21].

4.4 Growth plate biology

The growth-promoting effect of mecasermin on longitudinal bone growth is mediated through IGF-1R activation on chondrocytes in the epiphyseal growth plate. IGF-1R signaling stimulates chondrocyte proliferation in the proliferative zone, chondrocyte hypertrophy in the hypertrophic zone, and extracellular matrix synthesis (type II collagen, aggrecan). The composite effect drives endochondral ossification, the process by which cartilage is progressively replaced by bone at the growth plate, resulting in longitudinal skeletal growth [20, 21].

Under normal physiology, GH acts both directly on growth plate chondrocytes (stimulating local IGF-1 production in a paracrine manner) and indirectly through hepatic IGF-1 secretion (endocrine action). In patients with SPIGFD, both the paracrine and endocrine IGF-1 pathways are deficient. Exogenous mecasermin restores the endocrine component but does not fully replicate the paracrine or the direct (non-IGF-1-mediated) GH effects on the growth plate. This incomplete restoration is one explanation for the observation that growth responses to mecasermin in SPIGFD patients, while substantial, are generally less robust than growth responses to GH replacement in patients with isolated GH deficiency [9, 22].

4.5 Neurotrophic and neuroprotective activity

IGF-1 is a potent neurotrophic factor. IGF-1R is expressed on neurons and glial cells throughout the central and peripheral nervous systems. IGF-1R activation in neurons promotes neurite outgrowth, synaptogenesis, myelination, and neuronal survival through the PI3K/Akt anti-apoptotic pathway and through upregulation of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors [19, 23]. The neurotrophic properties of IGF-1 are the molecular basis for the investigational applications of mecasermin in Rett syndrome, amyotrophic lateral sclerosis, and other neurological disorders.

In the Rett syndrome context, MECP2 mutations reduce IGF-1 signaling in the central nervous system, and exogenous IGF-1 replacement has been shown to cross the blood-brain barrier (as evidenced by increased cerebrospinal fluid IGF-1 levels after subcutaneous mecasermin administration) and to ameliorate synaptic and behavioral deficits in MECP2-deficient mouse models [10, 23].

4.6 Metabolic effects

The metabolic pharmacology of mecasermin parallels insulin in several respects: stimulation of glucose uptake in skeletal muscle and adipose tissue, stimulation of amino acid incorporation into protein, stimulation of fatty acid uptake, suppression of hepatic glucose output, and suppression of lipolysis. However, mecasermin also suppresses insulin secretion from pancreatic beta cells (through IGF-1R-mediated signaling on islet cells), which partially offsets the hypoglycemic effect but can also contribute to glycemic dysregulation in certain contexts [4, 18]. The composite metabolic profile is anabolic and mildly hypoglycemic.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Mecasermin is administered exclusively by subcutaneous injection. The compound is well absorbed from the subcutaneous depot, with absolute bioavailability approaching 100 percent, consistent with the hydrophilic character and relatively small molecular weight (7649 daltons) of the protein, allowing efficient absorption through capillary fenestrations [4, 24]. Time to peak plasma concentration (Tmax) following subcutaneous injection is approximately 2 hours. Peak plasma IGF-1 concentrations are dose-proportional across the therapeutic dose range of 0.04 to 0.12 mg/kg [24].

Oral bioavailability is negligible owing to proteolytic degradation in the gastrointestinal tract. Intravenous administration has been used in research settings but is not an approved route. Intranasal and intrathecal routes have been explored in research for central nervous system delivery.

5.2 Distribution

The volume of distribution following subcutaneous administration in patients with severe primary IGF-1 deficiency is estimated at 0.257 (plus or minus 0.073) liters per kilogram at a dose of 0.045 mg/kg, with evidence that the volume of distribution increases modestly at higher doses [4, 24].

Distribution is critically governed by circulating IGF-binding proteins. In the systemic circulation, IGF-1 exists in three principal forms: free IGF-1 (less than 1 percent of total), binary complexes with IGF-binding proteins (IGFBP-1 through IGFBP-6, principally IGFBP-3, approximately 20 percent), and a 150-kilodalton ternary complex of IGF-1, IGFBP-3, and the acid-labile subunit (ALS, approximately 75 to 80 percent) [25]. The ternary complex is too large to cross capillary endothelium and serves as a circulating reservoir that extends the effective half-life of IGF-1 and limits its acute metabolic and mitogenic activity.

In patients with SPIGFD, IGFBP-3 and ALS concentrations are characteristically low (because their hepatic synthesis is also GH-dependent), resulting in a higher proportion of free and binary-complexed IGF-1 relative to total IGF-1 after mecasermin administration. This pharmacokinetic feature has two consequences: (1) the terminal half-life is shorter (approximately 5.8 hours versus approximately 19 hours in healthy individuals with normal binding protein levels), requiring twice-daily dosing; and (2) the peak free IGF-1 concentration is higher relative to total IGF-1, increasing the acute hypoglycemic signal [4, 24, 25].

5.3 Metabolism and elimination

Mecasermin, like endogenous IGF-1, is metabolized by lysosomal proteolysis principally in the liver and kidneys, with degradation to constituent amino acids. There is no hepatic cytochrome P450-mediated metabolism (the compound is a polypeptide, not a small molecule). Less than 0.1 percent of administered drug is excreted unchanged in urine [4].

The terminal elimination half-life in children with severe primary IGF-1 deficiency averages 5.8 hours. In healthy individuals with normal IGFBP-3 levels, the half-life extends to approximately 19.2 hours, reflecting the protective effect of the ternary complex against lysosomal degradation [4, 24]. Clearance of mecasermin is inversely proportional to IGFBP-3 concentration and is estimated at 0.04 liters per hour per kilogram at an IGFBP-3 level of 3 micrograms per milliliter.

Renal impairment is expected to reduce clearance modestly. Hepatic impairment may reduce clearance more substantially given the liver's role as the principal site of IGF-1 catabolism; however, formal pharmacokinetic studies in hepatic or renal impairment have not been published for mecasermin.

5.4 Routes of administration

The only approved route is subcutaneous injection (Increlex, 10 mg/mL solution). The compound is administered twice daily, shortly before or after a meal, at doses of 0.04 to 0.12 mg/kg per injection [4]. Injection sites should be rotated among the upper arm, thigh, buttock, and abdomen to minimize lipohypertrophy. Intravenous administration has been used in clinical research but is not registered and produces higher peak free IGF-1 concentrations with greater hypoglycemic risk. Intranasal delivery of a tripeptide fragment of IGF-1 (glycine-proline-glutamate, the N-terminal tripeptide cleavage product) has been explored for central nervous system delivery in neonatal brain injury research but is distinct from full-length mecasermin.

5.5 Special populations

The approved pediatric population is children with severe primary IGF-1 deficiency. Dosing is weight-based, beginning at 0.04 mg/kg twice daily and titrated to a maximum of 0.12 mg/kg twice daily based on growth response and tolerability. Adult pharmacokinetic data are limited; the compound is not approved for adult use. The pharmacokinetic profile in adults would be expected to differ from the pediatric SPIGFD population owing to differences in body composition, binding protein levels, and renal and hepatic function. Pregnancy and lactation data are absent; the compound is rated FDA pregnancy category C (animal reproduction studies have shown adverse effects; no adequate human studies).

6. Clinical Evidence Base

6.1 Severe primary IGF-1 deficiency (approved indication)

The regulatory approval of mecasermin was based on five single-arm, open-label clinical studies in pediatric patients with SPIGFD, conducted between the early 1990s and the mid-2000s, collectively enrolling 71 subjects with a mean treatment duration of 3.9 years (274 subject-years of exposure) [1, 9].

The pivotal efficacy analysis (Study 1419, N = 92 including later-enrolled subjects) demonstrated that first-year height velocity increased from a baseline mean (standard deviation) of 2.6 (1.7) centimeters per year to 8.0 (2.3) centimeters per year (p less than 0.0001). Height velocity declined modestly in subsequent years of treatment (a pattern consistent with GH replacement in GH-deficient patients) but remained substantially above the pre-treatment baseline. Height standard deviation score (SDS) showed progressive improvement, with a mean gain of approximately 1.9 SDS over 8 years of treatment [1, 9].

Chernausek, Backeljauw, and Frane published further observations on the long-term effects of rhIGF-1 in growth hormone insensitivity syndrome, confirming sustained height velocity improvement over a treatment period exceeding 10 years, with the most substantial gains occurring within the initial 5 years of therapy [22]. Hand and foot sizes improved significantly, especially when treatment was initiated early in childhood. However, treated patients with Laron syndrome were unlikely to reach adult heights in the normal reference range, partly due to the absence of direct (non-IGF-1-mediated) GH effects on growth plate chondrocytes and partly due to the incomplete pharmacokinetic replication of the physiological IGF-1 circadian and pulsatile release pattern [9, 22].

Guevara-Aguirre et al. (1995) reported results of a randomized, double-blind, placebo-controlled trial of rhIGF-1 replacement in 16 children from the Ecuadorian Laron syndrome population, demonstrating significant growth acceleration with mecasermin compared to placebo over 1 year [14].

6.2 Rett syndrome

Khawaja et al. (2014) conducted a Phase 1 clinical trial of mecasermin in 12 girls with MECP2 mutations (9 with Rett syndrome and 3 with related conditions) at Boston Children's Hospital [10]. The study included a 4-week multiple ascending dose period (0.04, 0.08, and 0.12 mg/kg twice daily) and a 20-week open-label extension at the maximum tolerated dose. Mecasermin reached the central nervous system compartment, as evidenced by increased cerebrospinal fluid IGF-1 concentrations at the end of the multiple ascending dose period. Apnea improved during the open-label extension, and neurobehavioral parameters (specifically measures of anxiety and

mood) also improved. The study was not powered for efficacy; the findings support further investigation of mecasermin in Rett syndrome. The FDA has granted orphan drug designation for mecasermin in this indication.

6.3 Amyotrophic lateral sclerosis

IGF-1 is a potent neurotrophic factor with neuroprotective properties in motor neuron culture systems, and early preclinical data supported investigation of rhIGF-1 in amyotrophic lateral sclerosis (ALS). Two randomized, placebo-controlled clinical trials of subcutaneous rhIGF-1 in ALS were conducted. The first (Lai et al. 1997) reported a modest slowing of functional decline in 266 patients treated with 0.1 mg/kg/day for 9 months [26]. A second larger trial (Sorenson et al. 2008, Mayo Clinic) administered IGF-1 for 2 years and found no significant improvement in muscle strength, daily functioning, or survival [11]. The ALS application has not advanced to regulatory approval, and the compound is not in active development for this indication.

6.4 Other investigational applications

Additional investigational contexts include Fragile X syndrome (orphan drug designation), SHANK3 gene deficiency syndrome (orphan drug designation), type 1 and type 2 diabetes mellitus (based on the metabolic actions of IGF-1, including insulin sensitization and beta-cell preservation), osteoporosis (based on the anabolic effects of IGF-1 on bone), and wound healing (based on the proliferative and angiogenic properties of IGF-1). Clinical evidence in these indications is early-stage, typically consisting of case reports, small open-label studies, or preclinical data. None has produced a controlled clinical trial of sufficient size and rigor to support regulatory submission [27].

7. Reported Research Dose Ranges

7.1 Approved doses

Severe primary IGF-1 deficiency (pediatric): Initial dose 0.04 mg/kg twice daily by subcutaneous injection, administered within 20 minutes of a meal or snack. Dose may be increased by 0.04 mg/kg per dose based on clinical response and tolerability, to a maximum of 0.12 mg/kg twice daily. If hypoglycemia occurs, the dose should be reduced and hypoglycemia managed with food intake. Treatment should not be initiated in patients who are unable to eat reliably [4].

7.2 Investigational doses

Rett syndrome (Phase 1): 0.04, 0.08, and 0.12 mg/kg twice daily by subcutaneous injection, corresponding to the approved dose range for SPIGFD [10].

Amyotrophic lateral sclerosis: 0.05 to 0.1 mg/kg/day by subcutaneous injection [11, 26].

Research applications (preclinical and translational): Doses vary widely depending on the animal model, route, and endpoint. In rodent studies, subcutaneous doses of 0.1 to 1.0 mg/kg/day are typical. Intracerebroventricular and intrathecal administration has been used in neonatal brain injury models at microgram-range doses.

Investigators should be aware that the pharmacokinetic profile of mecasermin is substantially influenced by IGFBP-3 levels, and that populations with normal IGFBP-3 (unlike the approved SPIGFD population) will have longer half-lives and potentially different dose-response relationships.

8. Sourcing and Quality Verification

Pharmaceutical-grade mecasermin (Increlex, Ipsen) is the highest-quality source for clinical research applications. The product is supplied as a sterile, preservative-containing (benzyl alcohol 9 mg/mL) aqueous solution at 10 mg/mL in 4-mL multiple-dose vials (40 mg per vial). Pharmaceutical sourcing requires prescription authorization in the United States and the European Union.

Research-grade recombinant human IGF-1 is available from multiple biological research suppliers (R&D Systems, PeproTech/Thermo Fisher, Sigma-Aldrich, GenScript, ProSpec, others) at greater than 95 percent purity by SDS-PAGE and reversed-phase HPLC. Supply is in microgram to milligram quantities, typically as lyophilized powder. Pricing is moderate for research use, in the range of \$100 to \$500 per milligram depending on supplier and quantity.

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

- SDS-PAGE under reducing and non-reducing conditions, confirming the expected molecular weight band at approximately 7.6 kilodaltons
- Reversed-phase high-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (7649 plus or minus 2 daltons for the intact polypeptide)
- Endotoxin testing (Limulus amebocyte lysate or recombinant factor C assay), especially for in vivo and cell culture applications; endotoxin should be less than 1 endotoxin unit per microgram of protein
- Bioactivity assay, typically a cell-based proliferation assay (MCF-7 cell line or other IGF-1R-expressing line) or a receptor phosphorylation assay, confirming biological activity consistent with the reference standard
- Disulfide bond integrity assessment by non-reducing SDS-PAGE or by peptide mapping, as incorrect disulfide pairing is the principal quality concern in *E. coli*-derived recombinant IGF-1 [5, 6]

Third-party analytical laboratories (SGS, Eurofins, Charles River, others) provide independent confirmation of vendor certificates of analysis. The research-grade rhIGF-1 market is well established, and material from reputable suppliers is generally reliable, but lot-to-lot variability in bioactivity has been reported and on-receipt analytical confirmation is appropriate for quantitative dose-response work.

9. Reconstitution and Handling

Pharmaceutical-grade mecasermin (Increlex) is supplied as a ready-to-use aqueous solution and requires no reconstitution. The product should be stored refrigerated at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) before and after opening. Vials should not be frozen. The product should be protected from direct light. After initial vial entry, the solution is stable for 30 days when stored refrigerated; unused material should be discarded after 30 days [4].

Research-grade recombinant human IGF-1 is typically supplied as a lyophilized powder and requires reconstitution before use. Recommended reconstitution procedures:

- Reconstitute in sterile water, phosphate-buffered saline (pH 7.4), or 10 millimolar hydrochloric acid (for concentrated stock solutions), depending on the supplier's instructions and the intended application
- Typical stock solution concentrations are 0.1 to 1.0 mg/mL
- Addition of a carrier protein (0.1 percent bovine serum albumin or human serum albumin) is recommended to prevent adsorptive losses to plasticware at low protein concentrations
- Stock solutions should be aliquoted into single-use volumes to avoid freeze-thaw cycles
- Lyophilized powder is stable at minus 20 degrees Celsius for the shelf life indicated by the supplier (typically 6 to 12 months from date of manufacture)
- Reconstituted stock solutions are stable at 2 to 8 degrees Celsius for up to 1 week and at minus 20 to minus 80 degrees Celsius for up to 3 months, depending on formulation buffer
- Repeated freeze-thaw cycles should be avoided; each cycle may reduce bioactivity by 5 to 15 percent depending on formulation
- Solutions should be inspected visually for particulate matter and discoloration prior to use; IGF-1 solutions should be clear and colorless

For parenteral research applications, sterile filtration (0.22-micrometer membrane filter) of reconstituted solutions is essential. The polypeptide is compatible with standard syringe materials (polypropylene, glass) but may adsorb to polycarbonate or certain other plastic surfaces in the absence of carrier protein.

10. Stack Interaction Considerations

Mecasermin interacts with several drug classes through its insulin-like metabolic pharmacology, its effects on the GH-IGF-1 axis, and its receptor-level signaling. Investigators conducting research with mecasermin, especially in chronic dosing regimens or in combination with other compounds, should consider:

Insulin and insulin secretagogues: Mecasermin has additive hypoglycemic effects with insulin (all formulations), sulfonylureas, and other insulin secretagogues. The combination substantially increases the risk of severe hypoglycemia and should be managed with careful glucose monitoring and dose adjustment. The prescribing information for Increlex recommends against concurrent use with insulin [4].

Growth hormone: Concurrent administration of GH and mecasermin is not recommended. In patients with SPIGFD due to GH receptor deficiency, GH is ineffective; concurrent use is redundant and does not augment the mecasermin response. In patients with other forms of IGF-1 deficiency, the combination has not been formally studied and the risk-benefit profile is undefined.

Glucocorticoids: Supraphysiological glucocorticoid doses suppress the GH-IGF-1 axis and antagonize the growth-promoting and anabolic effects of mecasermin. Concurrent chronic glucocorticoid therapy may reduce the efficacy of mecasermin in growth promotion applications. The interaction is pharmacodynamic and dose-dependent [27].

Oral hypoglycemic agents: Mecasermin may potentiate the hypoglycemic effects of metformin, thiazolidinediones, and other oral hypoglycemic agents through additive effects on glucose uptake and hepatic glucose output.

Anticoagulants: No direct pharmacokinetic interaction with warfarin or other anticoagulants has been established. However, as mecasermin is a protein and is not metabolized by hepatic cytochrome P450 enzymes, classical small-molecule drug-drug interactions mediated by enzyme inhibition or induction are not expected [4].

Other IGF-1 axis modulators: Concurrent use with IGF-1 analogs (IGF-1 LR3, IGF-1 DES), IGFBP modulators, or GH secretagogues (tesamorelin, sermorelin, ipamorelin) produces additive IGF-1R activation. The combination may exceed physiological IGF-1 levels and increase the risk of hypoglycemia, lymphoid tissue hypertrophy, and theoretical long-term mitogenic risk. Combinations of this type are common in non-clinical research but should be approached with attention to total IGF-1R activation.

mTOR inhibitors: Rapamycin (sirolimus) and its analogs (everolimus, temsirolimus) directly antagonize the mTORC1 signaling downstream of IGF-1R activation and would be expected to attenuate the growth-promoting and anabolic effects of mecasermin. This interaction is pharmacodynamically predictable and may be relevant in transplant patients or in oncology research contexts.

Cytochrome P450 interactions: As a polypeptide hormone, mecasecmin is not a substrate, inhibitor, or inducer of hepatic cytochrome P450 enzymes. Classical small-molecule CYP-mediated drug interactions are not applicable [4].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at approved doses in the SPIGFD population, based on clinical studies of 71 subjects treated for a mean duration of 3.9 years (274 subject-years), are [1, 4]:

- Hypoglycemia (42 percent of subjects reporting at least one episode). Severe hypoglycemia requiring assistance occurred in 5 subjects; hypoglycemic seizures or loss of consciousness occurred in 4 subjects. Hypoglycemia was most common in the first months of therapy and was generally avoided when mecasermin was administered within 20 minutes of a meal or snack.
- Tonsillar hypertrophy (15 percent), with lesser tonsillar growth in subsequent years of therapy. Adenoidal hypertrophy was also reported. Sleep-disordered breathing secondary to lymphoid tissue hypertrophy has been observed in some patients.
- Injection site lipohypertrophy (reported in multiple subjects; frequency not precisely quantified in published data). Managed by rotation of injection sites.
- Headache (reported by multiple subjects at moderate frequency).
- Arthralgia and myalgia (reported at low frequency).

No subjects withdrew from clinical studies because of adverse reactions.

11.2 Rare and serious adverse events

Intracranial hypertension (pseudotumor cerebri) with papilledema, visual changes, headache, nausea, and vomiting has been reported in 3 subjects. In 2 subjects, the events resolved without interruption of mecasermin treatment. Treatment was discontinued in the third subject. Intracranial hypertension has been reported as a class effect of growth-promoting agents (including GH) and is a labeled warning for Increlex [4].

Allergic reactions, including local and systemic hypersensitivity, have been reported rarely. Anaphylaxis has not been reported in clinical trials but cannot be excluded given the biologic nature of the product.

Lipohypertrophy at injection sites, when severe, may require surgical management in rare cases.

11.3 Theoretical long-term safety considerations

IGF-1R activation is mitogenic and anti-apoptotic. Epidemiological studies have reported associations between elevated circulating IGF-1 levels (in the upper quartile of the normal range) and increased risk of certain cancers (prostate, breast, colorectal) in the general population [28].

However, long-term follow-up of mecasermin-treated SPIGFD patients has not identified an increased incidence of malignancy at approved doses [1]. Conversely, the Ecuadorian Laron syndrome cohort (with congenital IGF-1 deficiency) shows near-complete absence of cancer over 25 years of follow-up, suggesting that lifelong IGF-1 deficiency is cancer-protective but not establishing that physiological IGF-1 replacement at therapeutic doses is cancer-promoting [13]. The labeled warning for Increlex advises monitoring for the development of neoplasms and recommends discontinuation if neoplasia is detected.

11.4 Pregnancy and lactation

Mecasermin is rated FDA pregnancy category C: animal reproduction studies have shown adverse effects at doses above the human therapeutic range, and adequate human studies have not been conducted. Use during pregnancy is not recommended. Data on excretion in human milk are not available; the compound should be used with caution during lactation [4].

11.5 Contraindications

Mecasermin is contraindicated in patients with closed epiphyses (the growth-promoting indication is limited to children with open growth plates), in patients with active or suspected neoplasia, and in neonates or infants (the benzyl alcohol preservative in the Increlex formulation is associated with a risk of serious adverse events, including "gasping syndrome," in premature neonates) [4].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative growth-promoting or IGF-1-axis compounds against mecasermin, 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 to represent the principal pharmacological strategies for modulating the GH-IGF-1 growth axis and to inform research-application decisions.

12.1 Somatropin (recombinant human growth hormone)

Mechanism: Direct replacement of growth hormone (GH). Somatropin binds the GH receptor on hepatocytes and other target cells, stimulating endogenous IGF-1 production, and exerts direct effects on growth plate chondrocytes, adipocytes, and muscle tissue [29].

Development trajectory: Somatropin was the first recombinant protein therapeutic (Genentech, FDA-approved 1985 as Protropin; methionyl form) and is approved for multiple indications: pediatric GH deficiency, Turner syndrome, chronic renal insufficiency, Prader-Willi syndrome, small for gestational age, idiopathic short stature, adult GH deficiency, and AIDS-related wasting. Multiple branded and biosimilar products are marketed worldwide [29].

Novelty: Low. Somatropin is the established standard of care for GH-responsive growth failure and has been in clinical use for over 40 years.

Effect size: First-year height velocity in GH-deficient children treated with somatropin is approximately 10 to 12 centimeters per year, compared to approximately 8 centimeters per year for mecasermin in SPIGFD patients. The greater growth response to somatropin reflects both the restoration of endocrine IGF-1 and the direct (non-IGF-1-mediated) GH effects on the growth plate [29].

Promising potential: Somatropin remains the standard of care for GH-responsive growth failure. It is not applicable to patients with SPIGFD (who are GH-insensitive by definition). Long-acting GH formulations (somapacitan, lonapegsomatropin, somatrogen) are in late-stage development or approved for once-weekly dosing [30].

Side-effect profile: Injection site reactions, headache, edema, arthralgia, myalgia, carpal tunnel syndrome (adults), rare intracranial hypertension, and glucose intolerance. The side-effect profile is generally favorable at approved doses. Theoretical long-term malignancy concerns are monitored but not established [29].

Overall validation: Very high. The most extensively validated growth-promoting compound in clinical medicine, with decades of clinical experience and multiple approved indications.

Comparison to mecasermin: Somatropin and mecasermin address different points in the GH-IGF-1 axis: somatropin replaces GH, while mecasermin replaces IGF-1. Somatropin is effective in GH-responsive patients; mecasermin is required for patients with defects at or below the GH receptor. The two are complementary rather than competitive. Mecasermin produces a smaller absolute growth response, attributable to the absence of direct GH effects and the pharmacokinetic limitations of twice-daily subcutaneous dosing versus the pulsatile endocrine pattern.

12.2 Lonapegsomatropin (TransCon hGH)

Mechanism: Prodrug of somatropin. Lonapegsomatropin is a transient PEGylation construct in which somatropin is covalently linked to a polyethylene glycol carrier through a proprietary linker that slowly releases unmodified somatropin over approximately one week, enabling once-weekly subcutaneous dosing [30].

Development trajectory: Ascendis Pharma developed lonapegsomatropin (Skytrofa), which received FDA approval in August 2021 for once-weekly treatment of pediatric GH deficiency. Phase 3 trials demonstrated non-inferiority to daily somatropin on annualized height velocity, with some analyses suggesting superiority [30].

Novelty: Moderate. The transient PEGylation technology is novel as a delivery platform; the active moiety is unmodified somatropin.

Effect size: Annualized height velocity in Phase 3 trials was approximately 11.2 centimeters per year at 52 weeks, comparable to or slightly above daily somatropin [30].

Promising potential: High. Once-weekly dosing substantially reduces injection burden and may improve adherence, a significant factor in pediatric growth failure treatment. The compound is not applicable to SPIGFD patients (same mechanism as somatropin).

Side-effect profile: Similar to daily somatropin, with injection site reactions, headache, and rare intracranial hypertension. No unique safety signals attributable to the PEGylation or linker [30].

Overall validation: High. FDA-approved with Phase 3 data supporting efficacy and safety.

Comparison to mecasermin: Lonapegsomatropin addresses the same GH-axis pathway as somatropin and is therefore complementary to, not competitive with, mecasermin. The once-weekly dosing convenience is a significant practical advantage over the twice-daily dosing of mecasermin, but the two compounds serve non-overlapping patient populations (GH-responsive versus GH-insensitive).

12.3 Mecasermin rinfabate (rhIGF-1/rhIGFBP-3 complex)

Mechanism: Equimolar complex of recombinant human IGF-1 and recombinant human IGFBP-3, designed to replicate the physiological binary complex and extend the circulating half-life of IGF-1 while reducing the proportion of free IGF-1 and the associated acute hypoglycemic signal [15, 31].

Development trajectory: Insmed Incorporated developed mecasermin rinfabate (IPLEX), which received FDA approval in December 2005 for the treatment of growth failure associated with severe primary IGF-1 deficiency. In March 2007, following a patent infringement settlement with Tercica and Genentech, Insmed ceased marketing IPLEX in the United States for growth-related indications. The European marketing authorization application was withdrawn. The product is no longer commercially available for growth failure [15].

Novelty: Moderate. The concept of delivering IGF-1 as a binding protein complex to modulate pharmacokinetics and safety is pharmacologically rational but was not demonstrated to produce clinically meaningful advantages over free mecasermin.

Effect size: Growth responses in clinical trials were comparable to those of mecasermin alone, though a higher daily IGF-1 dose equivalent was required to achieve comparable height SDS improvement (approximately 0.8 SDS over 2 years), suggesting that the IGFBP-3 complexation reduced the bioavailable IGF-1 fraction [15, 31].

Promising potential: Low. The product is no longer available for growth indications. Insmed explored development for HIV-associated adipose redistribution syndrome and myotonic muscular dystrophy but has not brought the product to market for any indication.

Side-effect profile: Reduced incidence and severity of hypoglycemia compared to free mecasermin in some analyses, consistent with the lower free IGF-1 fraction. Other adverse events were similar to mecasermin [15, 31].

Overall validation: Low to moderate. The compound was briefly FDA-approved but was withdrawn from the market for legal rather than safety or efficacy reasons. The clinical pharmacology is well characterized.

Comparison to mecasermin: Mecasermin rinfabate is the most directly comparable compound to mecasermin, sharing the same active moiety (rhIGF-1) with the addition of the IGFBP-3 carrier. The theoretical pharmacokinetic advantages (longer half-life, reduced hypoglycemia) were not consistently translated to superior clinical outcomes in growth promotion. Mecasermin remains the only commercially available IGF-1 replacement therapy. The mecasermin rinfabate experience informs current understanding of IGF-1 binding protein pharmacology but does not represent an active clinical alternative.

12.4 Tesamorelin (GHRH analog)

Mechanism: Synthetic analog of human growth hormone-releasing hormone (GHRH) with enhanced resistance to dipeptidyl aminopeptidase IV degradation, producing a longer effective half-life than native GHRH. Tesamorelin binds GHRH receptors on anterior pituitary somatotrophs and stimulates endogenous GH release, which in turn stimulates endogenous IGF-1 production [32].

Development trajectory: Theratechnologies developed tesamorelin (Egrifta), which received FDA approval in November 2010 for the reduction of excess abdominal fat (lipodystrophy) in HIV-infected patients with lipodystrophy. The compound is not approved for growth failure or IGF-1

deficiency [32].

Novelty: Moderate. The GHRH analog approach is mechanistically distinct from direct GH or IGF-1 replacement, preserving the pulsatile pattern of GH secretion and the physiological feedback regulation of the GH-IGF-1 axis.

Effect size: Tesamorelin increases serum GH and IGF-1 levels to approximately those observed with exogenous GH replacement and produces significant reduction in visceral adipose tissue in HIV-associated lipodystrophy. The compound has not been evaluated in growth failure indications and has no published data on height velocity in children [32].

Promising potential: Moderate for the approved lipodystrophy indication. Not applicable to SPIGFD patients (who have defects at or below the GH receptor and would not respond to increased GH secretion).

Side-effect profile: Injection site reactions (erythema, pruritus, pain), arthralgia, myalgia, peripheral edema, and glucose intolerance. The side-effect profile is consistent with the physiological effects of elevated GH and IGF-1 [32].

Overall validation: Moderate. FDA-approved for a non-growth indication. The GH-axis pharmacology is well characterized.

Comparison to mecasermin: Tesamorelin and mecasermin address fundamentally different pharmacological targets and patient populations. Tesamorelin stimulates endogenous GH secretion and is effective only in patients with an intact GH receptor and pituitary somatotroph function. Mecasermin bypasses the entire GH-IGF-1 signaling pathway and delivers the downstream effector directly. The two are not interchangeable for any indication.

12.5 IGF-1 LR3 (Long R3 IGF-1)

Mechanism: Synthetic IGF-1 analog in which the glutamic acid at position 3 is replaced with arginine and a 13-amino-acid N-terminal extension peptide is added. These modifications substantially reduce binding affinity for IGF-binding proteins (particularly IGFBP-3) while preserving full agonist activity at the IGF-1R, resulting in a higher proportion of free, bioactive IGF-1 in the circulation and a longer functional half-life [33].

Development trajectory: IGF-1 LR3 is a research reagent that has not been developed as a registered pharmaceutical. It is widely available from research-grade peptide suppliers and is used extensively in cell culture (as a serum-free medium supplement) and in preclinical research. The compound has no regulatory approval for any human indication [33].

Novelty: Low to moderate. The IGFBP-resistant IGF-1 analog concept is well established in the research literature. The compound is a research tool, not a clinical candidate.

Effect size: In vitro, IGF-1 LR3 produces greater and more sustained IGF-1R activation than native IGF-1 at equimolar concentrations, owing to the absence of binding protein sequestration. In vivo (preclinical), it produces greater anabolic and hypoglycemic effects at lower doses than native IGF-1. No clinical efficacy data exist [33].

Promising potential: Low as a clinical candidate (no regulatory pathway). High as a research tool for IGF-1R pharmacology, for serum-free cell culture, and for preclinical studies where sustained IGF-1R activation is desired.

Side-effect profile: No human safety data. The reduced IGFBP binding is predicted to increase the hypoglycemic and mitogenic risks relative to native mecasermin at equivalent IGF-1R occupancy levels.

Overall validation: Low. No clinical validation. Well characterized as a research reagent.

Comparison to mecasermin: IGF-1 LR3 is the principal research-grade alternative to mecasermin for in vitro and preclinical IGF-1R activation. It offers the practical advantage of sustained receptor activation without binding protein interference, which is valuable for cell culture and for mechanistic studies. However, the absence of clinical development, the lack of human safety data, and the enhanced mitogenic and hypoglycemic activity relative to native IGF-1 make it unsuitable as a clinical replacement for mecasermin. Mecasermin is the only clinically validated IGF-1 replacement therapy.

12.6 Comparator summary

The five comparators occupy distinct positions in the GH-IGF-1 axis pharmacology space. **Somatropin** is the gold standard for GH-responsive growth failure, with decades of clinical experience and the highest effect sizes on height velocity, but is ineffective in patients with SPIGFD. **Lonapegsomatropin** represents the most significant recent advance in GH delivery (once-weekly dosing), but addresses the same GH-responsive patient population. **Mecasermin rinfabate** is the most pharmacologically similar comparator, sharing the active moiety with mecasermin, but is no longer commercially available and did not demonstrate clinical superiority. **Tesamorelin** addresses a fundamentally different clinical application (lipodystrophy) through endogenous GH stimulation and is not applicable to SPIGFD. **IGF-1 LR3** is a research tool with enhanced pharmacological properties but no clinical development pathway.

Mecasermin occupies a unique and currently irreplaceable position as the only approved therapy for severe primary IGF-1 deficiency. No comparator can serve the SPIGFD patient population. The compound's positioning is defined less by competitive advantage against alternatives than by its role as the sole available therapy for a defined orphan population. For research applications, the principal practical alternatives are somatropin (for GH-responsive models), IGF-1 LR3 (for in vitro and preclinical IGF-1R activation), and tesamorelin (for GH-axis stimulation in non-SPIGFD contexts).

The investigational expansion of mecasermin into neuroprotective and neurodevelopmental applications (Rett syndrome, Fragile X syndrome, SHANK3 deficiency) represents a novel repositioning effort that is not replicated by any of the comparators. The neurotrophic properties of IGF-1, the demonstrated CNS penetration of subcutaneous mecasermin, and the orphan drug designations place mecasermin in a distinct investigational position for neurological indications. The success of this repositioning will depend on the outcomes of ongoing and planned clinical trials.

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