

RESEARCH MONOGRAPH . COMPOUND PROFILE

Mecasermin rinfabate

A recombinant equimolar binary protein complex of human IGF-1 and its principal binding protein IGFBP-3, developed by Insmed as iPLEX for subcutaneous replacement therapy in severe primary IGF-1 deficiency and subsequently investigated in amyotrophic lateral sclerosis and complications of extreme prematurity.

DOCUMENT	KDC-MN-1423
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Recombinant human insulin-like growth factor-1 and insulin-like growth factor binding protein-3 equimolar binary complex (rhIGF-1/rhIGFBP-3)

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ABSTRACT

Mecasermin rinfabate (International Nonproprietary Name; brand name iPLEX) is a pharmaceutical-grade equimolar binary complex of recombinant human insulin-like growth factor-1 (rhIGF-1, 70 amino acids, 7,649 Da) and recombinant human insulin-like growth factor binding protein-3 (rhIGFBP-3, 264 amino acids, approximately 28,700 Da unglycosylated), produced in *Escherichia coli* expression systems and formulated for subcutaneous injection at a combined molecular weight of approximately 36,381 daltons. The complex was designed to replicate the physiological binary association of IGF-1 with its most abundant circulating binding protein, thereby extending the plasma half-life of administered IGF-1 from approximately 10 to 20 minutes (free rhIGF-1) to approximately 13 to 21 hours (complexed form), reducing hypoglycemic risk relative to unbound IGF-1, and enabling once-daily subcutaneous dosing in contrast to the twice-daily regimen required for mecasermin (rhIGF-1 alone, marketed as Increlex). Upon subcutaneous administration, the binary complex associates with endogenous acid-labile subunit (ALS) to form the approximately 150 kDa ternary complex that represents the principal physiological reservoir of circulating IGF-1, thereby normalizing the IGF-1 axis in patients with deficient endogenous production.

The compound received United States Food and Drug Administration approval on December 12, 2005 (NDA 021884) for the treatment of growth failure in children with severe primary insulin-like growth factor-1 deficiency (Primary IGFD) or with growth hormone gene deletion who have developed neutralizing

antibodies to growth hormone. The approved dose range was 0.5 to 2.0 mg/kg administered once daily by subcutaneous injection, titrated to achieve physiological IGF-1 levels measured 8 to 18 hours post-dose. Clinical development was conducted in two cohort studies enrolling 36 children and adolescents with primary IGFD, predominantly growth hormone receptor deficiency (Laron syndrome), demonstrating statistically significant dose-dependent increases in height velocity from a pre-treatment baseline of approximately 3 to 4 cm/year to 6 to 9 cm/year during the first year of treatment.

The commercial trajectory of mecasermin rinfabate was truncated by patent litigation. In March 2007, Inmed Incorporated settled a patent infringement action brought by Tercica (the manufacturer of mecasermin/Increlex) by agreeing to withdraw iPLEX from the United States market for all short stature indications and to abandon its European regulatory application for these uses. The settlement extinguished the primary commercial indication. Inmed subsequently investigated mecasermin rinfabate in amyotrophic lateral sclerosis (ALS) under both clinical trial and compassionate-use frameworks; a Phase II randomized controlled trial in 330 ALS patients failed to demonstrate benefit on muscle strength, need for tracheostomy, or survival at the end of a two-year treatment period. More recently, the rhIGF-1/rhIGFBP-3 complex (under the development name of the successor product) has been investigated by Shire (now Takeda) and collaborators in extremely preterm infants for prevention of retinopathy of prematurity and other complications of prematurity, with a Phase 2 randomized controlled trial (NCT01096784) demonstrating a 53 percent decrease in severe bronchopulmonary dysplasia but no reduction in retinopathy of prematurity severity.

The pharmacology of mecasermin rinfabate is that of its constituent IGF-1 moiety acting through the type 1 IGF receptor (IGF-1R), a transmembrane receptor tyrosine kinase that activates the phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase (MAPK/ERK) signaling cascades to promote linear growth, cellular proliferation, differentiation, and survival. The IGFBP-3 moiety serves as a pharmacokinetic modulator, extending half-life and buffering against acute hypoglycemia, while also exerting IGF-independent effects including proapoptotic activity through nuclear receptor interactions and antiproliferative signaling in certain cellular contexts. The principal adverse events at approved doses are hypoglycemia (31 percent), headache (22 percent), arthralgia, injection site reactions, and lymphadenopathy. Safety data beyond 21 months of continuous treatment have not been established. This monograph reviews the molecular composition, development history, mechanism of action, pharmacokinetics, clinical evidence base across all studied indications, handling considerations, adverse-event profile, and a comparative assessment of five IGF-1 axis therapeutics against mecasermin rinfabate on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Mecasermin rinfabate.

United States Adopted Name: Mecasermin rinfabate.

Marketed name: iPLEX (Insmed Incorporated; United States). The brand name was used during the brief commercial period from December 2005 through March 2007 and continues to appear in the clinical and regulatory literature [1].

Development codes: SomatoKine (Celtrix Pharmaceuticals, the original development entity acquired by Insmed). The SomatoKine designation appears in the early development literature and in the original NDA submission materials [2].

Chemical Abstracts Service registry number: 792170-13-1 (complex). The individual components carry their own registry numbers: mecasermin (rhIGF-1) is CAS 68562-41-4; IGFBP-3 does not carry a standard CAS registry number as a standalone recombinant protein product in this context.

DrugBank identifier: DB14751.

NDA number: 021884 (United States Food and Drug Administration).

1.2 Structural class and composition

Mecasermin rinfabate is a non-covalent equimolar binary protein complex. It is not a small-molecule pharmaceutical; it is a recombinant protein therapeutic composed of two distinct polypeptide chains held together by non-covalent protein-protein interactions.

Component 1, rhIGF-1 (mecasermin): A single-chain polypeptide of 70 amino acids with three intramolecular disulfide bonds (Cys6-Cys48, Cys18-Cys61, Cys47-Cys52). Molecular weight: 7,649 daltons. The amino acid sequence is identical to mature human IGF-1. The protein is produced in *Escherichia coli* and is non-glycosylated [3].

Component 2, rhIGFBP-3: A single-chain polypeptide of 264 amino acids (mature form) with intramolecular disulfide bonds in the N-terminal and C-terminal domains. The unglycosylated molecular weight based on amino acid sequence is approximately 28,700 daltons; the E. coli-derived recombinant form used in mecasermin rinfabate is non-glycosylated, in contrast to the endogenous human protein which carries N-linked glycans and migrates at 40 to 53 kDa on SDS-PAGE [4, 5].

Complex molecular weight: Approximately 36,381 daltons (sum of rhIGF-1 at 7,649 Da and rhIGFBP-3 at approximately 28,732 Da).

Stoichiometry: 1:1 molar ratio of rhIGF-1 to rhIGFBP-3, representing the physiological binary complex that predominates in the circulation and that further associates with acid-labile subunit to form the approximately 150 kDa ternary complex [6].

Physical properties: Supplied as a clear, colorless to slightly opalescent sterile solution for subcutaneous injection. The formulation contains sodium chloride, benzyl alcohol (as preservative), sodium succinate buffer, and polysorbate 20. The concentration in the marketed formulation was 36 mg/mL (approximately 1 micromolar complex) in multi-dose vials [1].

1.3 Biosynthesis and manufacturing

Both protein components are produced individually by recombinant DNA technology in *Escherichia coli* expression systems. The rhIGF-1 component is expressed as a fusion protein or inclusion body, solubilized, refolded to achieve correct disulfide pairing, and purified by chromatographic methods including ion exchange and reversed-phase high-performance liquid chromatography [3, 7]. The rhIGFBP-3 component is similarly expressed in *E. coli*, refolded, and purified. The two purified proteins are combined under controlled conditions to allow spontaneous non-covalent complexation at equimolar stoichiometry, and the resulting binary complex is formulated for injection [8].

The manufacturing process was developed originally by Celtrix Pharmaceuticals using proprietary protein production technology, subsequently transferred to Inmed Incorporated upon acquisition, and covered by United States Patent 7,968,679 describing purified rhIGF-1/rhIGFBP-3 complexes and their method of manufacture [8].

2. Abstract

Mecasermin rinfabate (iPLEX, SomatoKine) is a recombinant protein therapeutic consisting of equimolar human IGF-1 complexed with its principal circulating binding protein IGFBP-3, developed to provide physiological IGF-1 replacement therapy with improved pharmacokinetic properties relative to unbound rhIGF-1 (mecasermin/Increlex). The complex mimics the naturally occurring binary association of IGF-1 and IGFBP-3 that constitutes the first step in ternary complex formation with the acid-labile subunit, thereby prolonging plasma half-life from minutes to approximately 13 to 21 hours and enabling once-daily subcutaneous administration [9, 10].

The compound was approved by the FDA in December 2005 for growth failure in severe primary IGF-1 deficiency (Laron syndrome, growth hormone gene deletion with neutralizing antibodies). Clinical data from two cohort studies in 36 children demonstrated dose-dependent increases in height velocity with a favorable safety profile relative to free rhIGF-1, including a lower incidence of hypoglycemia (31 percent versus 42 percent for mecasermin alone) [1, 11]. The once-daily dosing schedule represented a practical advantage over the twice-daily requirement for mecasermin.

The commercial life of mecasermin rinfabate was terminated in March 2007 by a patent infringement settlement with Tercica, the manufacturer of mecasermin (Increlex). Under the settlement terms, Insmad withdrew iPLEX from the United States market for all short stature indications and abandoned its European regulatory submission [12]. The compound was subsequently made available under investigational new drug frameworks for amyotrophic lateral sclerosis, where a Phase II trial in 330 patients failed to demonstrate efficacy [13, 14]. More recent clinical investigation of the rhIGF-1/rhIGFBP-3 complex has focused on prevention of complications in extremely preterm infants, with a Phase 2 randomized controlled trial demonstrating reduction in severe bronchopulmonary dysplasia but not in retinopathy of prematurity [15].

The pharmacological mechanism is IGF-1 receptor activation promoting linear growth through stimulation of growth plate chondrocyte proliferation and differentiation, with additional anabolic, insulin-sensitizing, and neuroprotective activi-

ties. The IGFBP-3 component modulates pharmacokinetics, buffers against hypoglycemia, and may contribute independent antiproliferative and proapoptotic signaling in certain tissues [4, 5]. Principal adverse events at therapeutic doses include hypoglycemia, headache, arthralgia, and injection site reactions. The compound is no longer commercially available for any indication as of the current monograph revision.

3. Discovery and Development History

3.1 Origin and rationale

The development of mecasermin rinfabate arose from the recognition that free (unbound) IGF-1 administered as a therapeutic has unfavorable pharmacokinetic properties, including rapid renal clearance (half-life approximately 10 to 20 minutes for free IGF-1), dose-limiting hypoglycemia from insulin receptor cross-activation at supraphysiological free IGF-1 concentrations, and the requirement for twice-daily subcutaneous injection [16]. Under normal physiology, greater than 99 percent of circulating IGF-1 exists in protein-bound states, with approximately 75 to 80 percent bound in the 150 kDa ternary complex (IGF-1 plus IGFBP-3 plus acid-labile subunit) and the remainder in approximately 50 kDa binary complexes with various IGFBPs. The ternary complex serves as the principal reservoir, extending IGF-1 half-life to 12 to 15 hours and preventing hypoglycemia by restricting vascular egress and insulin receptor access [6, 16].

Celtrix Pharmaceuticals (San Jose, California) developed the concept of administering IGF-1 pre-complexed with its principal binding protein IGFBP-3, reasoning that subcutaneous injection of the binary complex would (a) extend plasma half-life by enabling ternary complex formation with endogenous ALS; (b) reduce hypoglycemic risk by buffering free IGF-1 concentrations; and (c) permit once-daily dosing. The development compound was designated SomatoKine [2].

3.2 Preclinical development

Pharmacokinetic studies in rats demonstrated approximately 85 percent bioavailability after intramuscular administration and approximately 50 percent after subcutaneous administration of the rhIGF-1/rhIGFBP-3 complex, with a subcutaneous half-life substantially longer than free rhIGF-1 [17]. Primate pharmacokinetic studies confirmed the extended half-life profile and the formation of ternary complex with endogenous ALS following subcutaneous dosing. Toxicology studies in multiple species did not identify dose-limiting toxicities at the proposed clinical dose range.

3.3 Acquisition by Inmed and clinical development

Inmed Incorporated (Richmond, Virginia) acquired the SomatoKine program from Celtrix and advanced the compound through Phase I pharmacokinetic studies in healthy volunteers, Phase II dose-ranging studies in children with growth hormone insensitivity syndrome (GHIS), and the pivotal cohort studies that supported the NDA submission [2, 9]. In January 2005, Inmed submitted NDA 021884 to the FDA. The FDA approved iPLEX on December 12, 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone [1].

3.4 Patent litigation and market withdrawal

Tercica, Inc. (South San Francisco, California), the manufacturer of mecasermin (Increlex, unbound rhIGF-1), filed patent infringement claims against Inmed alleging that iPLEX infringed patents licensed to Tercica covering the use of IGF-1 for treatment of growth disorders. Litigation proceeded in both United States and United Kingdom courts. In March 2007, following a jury verdict finding infringement, Inmed settled by agreeing to cease selling iPLEX in the United States for severe primary IGFD and all short stature indications, to withdraw its European marketing application for these uses, and to restructure its commercial operations [12]. The settlement effectively terminated the primary commercial trajectory of mecasermin rinfabate.

3.5 Post-withdrawal investigation in ALS

Following the patent settlement, Inmed retained rights to investigate mecasermin rinfabate in non-growth indications. IGF-1 had shown neuroprotective activity in preclinical models of motor neuron degeneration, and two earlier Phase III trials of free rhIGF-1 in ALS had produced inconsistent results (one North American trial positive, one European trial negative) [13, 14]. In March 2009, the FDA authorized access to the remaining supply of iPLEX for Americans with ALS under both clinical trial and single-patient compassionate-use IND frameworks. A Phase II randomized, double-blind, placebo-controlled trial enrolled 330 ALS patients at 20 centers in the United States, with subcutaneous mecasermin rinfabate administered for two years. The trial failed to demonstrate benefit on muscle strength, need for tracheostomy, or survival, and the ALS development program was discontinued [13, 14].

3.6 Successor development in neonatal medicine

The rhIGF-1/rhIGFBP-3 concept was subsequently pursued by Premacure AB (later acquired by Shire, then Takeda) for prevention of retinopathy of prematurity and other complications in extremely preterm infants, where postnatal IGF-1 deficiency contributes to impaired vascular and neurological development [15, 18]. This program, using intravenous administration of the complex to maintain physiological IGF-1 levels, represents the principal ongoing clinical investigation of the rhIGF-1/rhIGFBP-3 mechanism as of the current monograph revision.

4. Mechanism of Action

4.1 IGF-1 receptor activation

The pharmacological activity of mecasermin rinfabate is mediated primarily through the type 1 insulin-like growth factor receptor (IGF-1R), a transmembrane receptor tyrosine kinase composed of two extracellular alpha subunits and two transmembrane beta subunits linked by disulfide bonds. The IGF-1R is expressed on virtually all cell types but is present at particularly high density on growth plate chondrocytes, osteoblasts, skeletal muscle cells, hepatocytes, and neurons [19, 20].

Upon binding of IGF-1 to the extracellular alpha subunit, the receptor undergoes autophosphorylation on tyrosine residues in the intracellular beta subunit kinase domain, creating docking sites for insulin receptor substrate (IRS) proteins and Src homology collagen (Shc) adaptor proteins. Two principal downstream signaling cascades are activated [19, 20]:

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway mediates cell survival, protein synthesis (through mTOR activation), glucose uptake, and glycogen synthesis. In growth plate chondrocytes, PI3K/Akt signaling promotes both proliferation and differentiation and interacts with the parathyroid hormone-related peptide/Indian hedgehog (PTHrP/Ihh) pathway that regulates endochondral ossification [21].

The Ras/MAPK/ERK pathway mediates mitogenic signaling, cellular proliferation, and gene expression changes. In growth plate chondrocytes, the MAPK pathway is the principal mediator of IGF-1-stimulated cell division [21].

4.2 Growth plate effects

The primary therapeutic mechanism in severe primary IGF-1 deficiency is restoration of growth plate chondrocyte proliferation. In the normal growth plate, IGF-1 produced locally (autocrine/paracrine) and delivered from the circulation (endocrine) stimulates clonal expansion of proliferative zone chondrocytes, promotes

hypertrophic differentiation, and stimulates extracellular matrix synthesis. In states of IGF-1 deficiency (Laron syndrome, GH gene deletion), growth plate activity is markedly reduced, resulting in severe growth failure [22, 23].

Administration of mecasermin rinfabate restores circulating IGF-1 levels to the physiological range, enabling both endocrine delivery to the growth plate and restoration of hepatic IGF-1 axis signaling. The IGFBP-3 component ensures that IGF-1 delivery occurs in a sustained, buffered manner that approximates normal physiology rather than producing the acute spikes and rapid clearance characteristic of free IGF-1 administration [9, 16].

4.3 Role of IGFBP-3 in the complex

IGFBP-3 in the mecasermin rinfabate complex serves multiple functions beyond simple pharmacokinetic extension [4, 5]:

Pharmacokinetic buffering. By binding IGF-1 with high affinity (Kd approximately 0.1 to 1 nM), IGFBP-3 prevents renal filtration of the small (7.6 kDa) IGF-1 molecule and restricts vascular egress, maintaining a sustained plasma reservoir. Upon subcutaneous injection, the binary complex recruits endogenous acid-labile subunit to form the approximately 150 kDa ternary complex that is too large for glomerular filtration or capillary transit [6].

Hypoglycemia mitigation. Free IGF-1 cross-activates the insulin receptor (approximately 100-fold lower affinity than insulin but sufficient at supraphysiological concentrations), producing dose-limiting hypoglycemia. IGFBP-3 binding restricts IGF-1 access to the insulin receptor, reducing hypoglycemic risk relative to equimolar free IGF-1 [11, 16].

IGF-independent signaling. IGFBP-3 possesses intrinsic biological activities independent of IGF-1 carriage, including proapoptotic signaling through interaction with retinoid X receptor alpha (RXRalpha) and Nur77, antiproliferative effects mediated through cell-surface association, and modulation of transforming growth factor beta (TGF-beta) signaling [4, 5]. These activities may be relevant in the neonatal and neuroprotective contexts where the complex is being investigated but are not the primary therapeutic mechanism in the growth-failure indication.

4.4 Insulin-like metabolic effects

IGF-1 produces insulin-like metabolic effects at physiological and supraphysiological concentrations, including stimulation of glucose uptake in skeletal muscle and adipose tissue, suppression of hepatic glucose output, promotion of protein synthesis, and inhibition of proteolysis [16]. These effects contribute to the growth-promoting activity (anabolism) but also underlie the hypoglycemic adverse-event signal. The insulin-like effects are mediated through both the IGF-1R (which shares downstream signaling with the insulin receptor) and through direct insulin receptor activation at high free IGF-1 concentrations.

4.5 Neuroprotective mechanisms

The rationale for investigation in ALS and neonatal neuroprotection rests on the neurotrophic and neuroprotective activities of IGF-1 signaling. IGF-1R activation in motor neurons, cortical neurons, and oligodendrocytes promotes cell survival (through PI3K/Akt-mediated inhibition of apoptosis), axonal growth, synaptic plasticity, and myelination [24, 25]. IGF-1 promotes oligodendrocyte proliferation, differentiation, and myelin synthesis. In models of traumatic brain injury and ischemic stroke, IGF-1 administration reduces infarct volume and promotes functional recovery [24, 25]. IGFBP-3 facilitates IGF-1 transport across the blood-brain barrier through a carrier-mediated system [25].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Mecasermin rinfabate is administered by subcutaneous injection. Bioavailability after subcutaneous administration is approximately 50 percent based on primate pharmacokinetic data, and approximately 85 percent after intramuscular injection in rats [17]. The lower subcutaneous bioavailability relative to intramuscular reflects slower absorption from subcutaneous tissue with some local proteolytic degradation.

Time to peak plasma IGF-1 concentration after subcutaneous injection of 0.5 to 2.0 mg/kg mecasermin rinfabate in children with growth hormone insensitivity syndrome is approximately 12 to 18 hours, reflecting slow absorption from the subcutaneous depot and sustained release into the circulation [9, 10].

5.2 Distribution

Following subcutaneous absorption, the binary complex of rhIGF-1 and rhIGFBP-3 enters the circulation and associates with endogenous acid-labile subunit (ALS) to form the approximately 150 kDa ternary complex. In patients with growth hormone insensitivity syndrome who have intact ALS production, this ternary complex formation extends the effective half-life and creates a large circulating reservoir. Patients with undetectable ALS levels (indicating more severe GH axis disruption) show somewhat shorter half-lives and lower peak IGF-1 levels at equivalent doses [1, 10].

The volume of distribution is restricted by the large molecular size of the ternary complex, which is confined predominantly to the vascular and extravascular fluid compartments. Tissue penetration of IGF-1 occurs upon dissociation from binding proteins, with delivery to target tissues (growth plate, muscle, liver, central nervous system) governed by local IGFBP protease activity and receptor density.

5.3 Metabolism and elimination

The IGF-1 half-life after subcutaneous mecasermin rinfabate administration in children with GHIS is approximately 13 to 21 hours, compared to approximately 5.8 hours for free rhIGF-1 (mecasermin) in the same patient population [9, 10]. The extended half-life reflects ternary complex formation with ALS.

Elimination proceeds by proteolytic degradation following dissociation from binding proteins. IGFBPs are cleaved by specific proteases (including PAPP-A, matrix metalloproteinases, and cathepsins) that release IGF-1 for receptor binding or further degradation. The released IGF-1 undergoes proteolytic catabolism in peripheral tissues and renal filtration of fragments. The IGFBP-3 component is similarly degraded by proteases, with fragments cleared by hepatic and renal mechanisms [6].

In preterm infants receiving intravenous rhIGF-1/rhIGFBP-3, the IGF-1 half-life is substantially shorter (approximately 0.8 to 2 hours), reflecting immature ternary complex formation due to low endogenous ALS levels in this population and necessitating continuous intravenous infusion [18, 26].

5.4 Special populations

Patients with detectable versus undetectable ALS. Mean height velocity in the clinical cohorts was 8.1 cm/year for subjects with detectable ALS versus 6.3 cm/year for subjects with undetectable ALS at equivalent doses, reflecting the contribution of ternary complex formation to drug exposure and efficacy [1, 10].

Preterm infants. The immature IGF axis in extremely preterm infants (23 to 28 weeks gestational age) results in low endogenous ALS and IGFBP-3, producing rapid clearance of administered complex and requiring continuous intravenous infusion at 250 micrograms/kg/24 hours to maintain target IGF-1 levels [15, 18, 26].

5.5 Routes of administration

Subcutaneous injection (approved route). Once-daily subcutaneous injection at 0.5 to 2.0 mg/kg. The injection should be administered at approximately the same time each day, and the patient must eat within a reasonable timeframe of the injection to mitigate hypoglycemic risk [1].

Intravenous infusion (investigational). Continuous intravenous infusion at 250 micrograms/kg/24 hours has been used in the preterm infant trials, initiated within 24 hours of birth and continued to postmenstrual age 29 weeks and 6 days [15].

6. Preclinical Pharmacology

6.1 Growth studies in animal models

Preclinical studies in hypophysectomized rats demonstrated that subcutaneous rhIGF-1/rhIGFBP-3 complex produced dose-dependent increases in body weight, tibial epiphyseal width (a marker of growth plate expansion), and organ growth comparable to free rhIGF-1 at equimolar IGF-1 doses but with reduced hypoglycemia and improved tolerability [17, 27]. The complex produced sustained elevations in circulating IGF-1 with lower peak-to-trough ratios than free rhIGF-1, consistent with the extended half-life pharmacokinetic profile.

6.2 Neuroprotection models

In rodent models of motor neuron degeneration, ischemic stroke, and traumatic brain injury, IGF-1 (administered as free peptide or as IGF-1/IGFBP-3 complex) demonstrated neuroprotective activity including reduction of infarct volume, promotion of motor neuron survival, stimulation of myelination, and improvement of functional outcomes [24, 25]. The IGFBP-3 component facilitated central nervous system penetration through carrier-mediated blood-brain barrier transport. These preclinical findings provided the rationale for the ALS clinical program.

6.3 Neonatal models

In neonatal animal models, IGF-1 deficiency following premature separation from maternal/placental IGF-1 supply was shown to impair retinal vascularization, lung maturation, and brain development. Replacement with rhIGF-1/rhIGFBP-3 to maintain physiological IGF-1 levels prevented or attenuated retinal neovascularization pathology, promoted surfactant production and alveolar development, and supported oligodendrocyte maturation [15, 18]. These findings provided the rationale for the Phase 2 preterm infant trial.

6.4 Metabolic effects

In diabetic and insulin-resistant rodent models, rhIGF-1/rhIGFBP-3 produced insulin-sensitizing effects including improved glucose tolerance, reduced hyperinsulinemia, and improved insulin receptor signaling in skeletal muscle, with a lower hypoglycemic risk profile than equimolar free rhIGF-1 [27]. These findings supported early-stage investigation of the complex for type 2 diabetes, though this indication was not advanced to clinical development.

7. Clinical Evidence Base

7.1 Severe primary IGF-1 deficiency (approved indication)

The FDA approval of iPLEX was based on two prospective cohort studies enrolling a total of 36 children and adolescents with primary IGFD [1, 10]. The study population included 32 subjects (89 percent) with growth hormone receptor deficiency (Laron syndrome), 3 subjects (8 percent) with GH gene deletion and neutralizing antibodies to exogenous GH, and 1 subject with primary IGFD of unknown etiology.

Subjects received mecasermin rinfabate at doses titrated from 0.5 mg/kg/day to therapeutic range of 1.0 to 2.0 mg/kg/day by subcutaneous injection once daily, with dose adjusted based on IGF-1 levels measured 8 to 18 hours post-dose. The primary efficacy measure was height velocity (growth rate) during treatment compared to pre-treatment baseline.

Results demonstrated statistically significant, dose-dependent increases in height velocity [10]. Mean height velocity during months 0 to 6 was 8.1 cm/year for subjects with detectable ALS levels on the higher dose (approximately 1.0 mg/kg/day) and 9.1 cm/year at 2.0 mg/kg/day, compared to pre-treatment growth rates of approximately 3 to 4 cm/year. The growth response was sustained through the available follow-up period. Subjects with undetectable ALS showed somewhat lower responses (6.3 cm/year), consistent with impaired ternary complex formation and reduced drug exposure [1, 10].

7.2 Comparison with mecasermin (Increlex)

No head-to-head randomized controlled trials comparing mecasermin rinfabate with mecasermin have been published. Cross-study comparisons suggest similar efficacy in promoting linear growth in primary IGFD, with mecasermin rinfabate offering practical advantages (once-daily versus twice-daily dosing) and a somewhat lower incidence of hypoglycemia (31 percent versus 42 percent) [11]. However, preliminary uncontrolled studies suggested that the complex failed to demonstrate an improvement in growth rate compared to treatment with rhIGF-1 alone, despite achieving extension of serum IGF-1 half-life and normalization of serum IGF-1 levels [28].

7.3 Amyotrophic lateral sclerosis

The ALS clinical program was initiated following the patent settlement that removed the growth-failure indication. Two earlier Phase III trials of free rhIGF-1 in ALS had produced conflicting results: a North American trial (Lai et al. 1997) reported modest slowing of functional decline, while a European trial (Borasio et al. 1998) failed to confirm benefit [13, 14].

The Phase II trial of mecasermin rinfabate enrolled 330 ALS patients at 20 centers in the United States in a randomized, double-blind, placebo-controlled design with subcutaneous administration for two years. The trial was funded by the Muscular Dystrophy Association and the National Institutes of Health and conducted through the University of Rochester. At trial completion, there were no differences between the mecasermin rinfabate and placebo groups in muscle strength, need for tracheostomy, or survival [13, 14]. The negative result was conclusive and the program was discontinued.

In March 2009, the FDA authorized compassionate use of the remaining iPLEX supply for individual ALS patients through single-patient IND applications, given the absence of effective therapies for the disease. This supply was described as "very limited" [14].

7.4 Retinopathy of prematurity and complications of extreme prematurity

A Phase 2 randomized controlled trial (NCT01096784) conducted from September 2014 to March 2016 evaluated rhIGF-1/rhIGFBP-3 for prevention of retinopathy of prematurity (ROP) and other complications in extremely preterm infants born at 23 0/7 to 27 6/7 weeks gestational age [15]. Infants were randomly allocated to rhIGF-1/rhIGFBP-3 (250 micrograms/kg/24 hours by continuous intravenous infusion from less than 24 hours of birth to postmenstrual age 29 weeks and 6 days) or standard neonatal care, with follow-up to postmenstrual age 40 weeks and 4 days.

The primary endpoint (decrease in ROP severity) was not met. However, secondary endpoints demonstrated a 53 percent decrease in severe bronchopulmonary dysplasia in the full analysis set (21.3 percent treated versus 44.9 percent standard care) and an 89 percent decrease in the evaluable set (4.8 percent versus

44.9 percent; $p = 0.02$). A nonsignificant trend toward decreased grades 3 to 4 intraventricular hemorrhage was also observed (13.1 percent versus 23.3 percent in the full analysis set) [15].

These findings support the concept that physiological IGF-1 replacement in extremely preterm infants may protect against lung injury and potentially brain injury, even though the retinal vascularization endpoint was not achieved. Further clinical development in this population is ongoing under successor sponsorship (Shire/Takeda).

7.5 Other investigated indications

Early-stage investigation of mecasermin rinfabate was conducted in several additional contexts that did not advance to definitive clinical trials:

Myotonic dystrophy. Pilot studies evaluated IGF-1/IGFBP-3 for the catabolic and myopathic features of myotonic dystrophy type 1. Published results are limited to conference abstracts.

Type 2 diabetes and insulin resistance. The insulin-sensitizing properties of the complex provided rationale for investigation in metabolic disease, but this program was not advanced beyond early Phase 1 after the patent settlement constrained Insmed's commercial resources.

HIV-associated wasting. IGF-1 axis replacement for anabolic therapy in HIV-associated cachexia was explored in the early development literature but was not formally developed as a clinical program.

8. Sourcing and Quality Verification

Mecasermin rinfabate (iPLEX) is no longer commercially manufactured or marketed for any indication. The compound is not available from the original manufacturer (Inmed) or through pharmaceutical distribution channels. Research access to the rhIGF-1/rhIGFBP-3 complex requires one of the following approaches:

Custom synthesis. Recombinant production of both rhIGF-1 and rhIGFBP-3 in *E. coli* expression systems followed by in vitro complex formation is feasible for research applications. Published protocols describe *E. coli* Origami B (DE3) as a preferred expression host for mecasermin production, with expression levels approximately twice those achieved in BL21 (DE3) [7]. Reconstitution of the binary complex requires equimolar mixing under controlled buffer conditions.

Individual components. Research-grade rhIGF-1 is available from multiple suppliers (PeproTech, R&D Systems, Sigma-Aldrich, and others) at greater than 95 percent purity. Research-grade rhIGFBP-3 is similarly available, though at higher cost and lower availability than rhIGF-1. Investigators may prepare the binary complex from individual components for in vitro or preclinical research.

Clinical-grade successor products. The rhIGF-1/rhIGFBP-3 complex continues in clinical development under successor programs (Shire/Takeda) for neonatal indications. Access for clinical research is through the sponsor's clinical trial framework.

Quality verification for research-prepared complex should include:

- SDS-PAGE confirmation of both components at expected molecular weights
- Size-exclusion chromatography confirmation of binary complex formation
- Bioactivity assay (IGF-1R phosphorylation in responsive cells)
- Endotoxin testing for any in vivo application
- Mass spectrometry confirmation of protein identity
- Circular dichroism or other structural confirmation of correct protein folding

9. Reconstitution and Handling

9.1 Marketed formulation (historical)

The marketed iPLEX formulation was supplied as a ready-to-use sterile solution at 36 mg/mL in multi-dose glass vials containing sodium chloride, sodium succinate buffer, polysorbate 20, and benzyl alcohol (9 mg/mL) as a preservative. The formulation required refrigerated storage at 2 to 8 degrees Celsius and protection from light. Once a vial was entered, it was stable for 30 days when stored under refrigerated conditions [1].

9.2 Research-grade handling

For research applications using custom-prepared or individually sourced components:

Storage of lyophilized proteins. Both rhIGF-1 and rhIGFBP-3 are stable as lyophilized powders at minus 20 to minus 80 degrees Celsius for extended periods (years). Avoid repeated freeze-thaw cycles of reconstituted material.

Reconstitution. Reconstitute lyophilized proteins in appropriate buffer (phosphate-buffered saline or manufacturer-recommended buffer) to desired concentration. Typical stock concentrations are 100 to 1000 micrograms/mL for each component.

Complex formation. Mix equimolar amounts of rhIGF-1 and rhIGFBP-3 in neutral pH buffer (pH 6.5 to 7.5) at room temperature for 30 to 60 minutes. Complex formation is spontaneous and driven by the high-affinity interaction (K_d approximately 0.1 to 1 nM). Confirm complex formation by size-exclusion chromatography if quantitative stoichiometry is required.

Storage of reconstituted complex. Store at 2 to 8 degrees Celsius for short-term use (up to 7 days) or aliquot and freeze at minus 80 degrees Celsius for longer storage. Avoid repeated freeze-thaw cycles. The presence of a carrier protein (0.1 percent bovine serum albumin) improves stability at low concentrations.

Compatibility. The protein complex is incompatible with strong acids, strong bases, and organic solvents. For intravenous research applications, compatibility with standard neonatal infusion solutions (glucose, amino acid solutions) has been confirmed for the clinical formulation [29].

10. Stack Interactions and Combinations

Mecasermin rinfabate interactions arise primarily from the IGF-1 component's metabolic activity and from competitive interactions within the IGF axis. Investigators conducting research with the complex, particularly in chronic dosing or combination protocols, should consider:

Growth hormone. Concurrent growth hormone administration is pharmacologically redundant in patients with GH insensitivity (the approved indication) since these patients cannot respond to GH. In patients with partial GH sensitivity or in research contexts with intact GH axis, concurrent GH would increase endogenous IGF-1 production additively. The combination is not clinically relevant to the approved patient population.

Insulin and insulin analogs. Concurrent insulin and mecasermin rinfabate produce additive hypoglycemic risk. Dose adjustment of insulin may be required. The IGF-1 component produces insulin-sensitizing effects that may reduce insulin requirements in insulin-resistant states.

Oral hypoglycemic agents. Sulfonylureas and meglitinides increase hypoglycemic risk when combined with mecasermin rinfabate. Metformin does not directly increase hypoglycemic risk but the combination has not been studied.

Glucocorticoids. Chronic glucocorticoid therapy suppresses the GH/IGF-1 axis and may attenuate the growth-promoting effects of mecasermin rinfabate. Glucocorticoids also antagonize the insulin-sensitizing effects of IGF-1. The interaction is pharmacodynamic rather than pharmacokinetic.

Other IGF axis therapeutics. Concurrent mecasermin (free rhIGF-1) and mecasermin rinfabate would produce additive IGF-1 exposure with increased hypoglycemic risk. The combination is not clinically indicated.

Anticoagulants. No characterized pharmacokinetic interactions. The protein complex does not interact with cytochrome P450 metabolism.

Cytochrome P450 substrates. Mecasermin rinfabate is a protein therapeutic degraded by proteolysis; it does not interact with cytochrome P450 enzymes and is not expected to produce pharmacokinetic drug-drug interactions with small-molecule therapeutics.

Nutritional status. Adequate caloric and protein intake is essential for IGF-1 anabolic activity. The compound should not be administered in fasting states due to hypoglycemic risk. The product label recommends that patients eat within a reasonable timeframe of injection and not receive the drug if they skip a meal [1].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in the clinical development program at approved doses (0.5 to 2.0 mg/kg/day subcutaneous) include [1, 11]:

- Hypoglycemia (31 percent; lower than the 42 percent reported for mecasermin alone, but still the most common adverse event)
- Headache (22 percent)
- Injection site reactions (local erythema, pain, induration)
- Arthralgia and bone pain
- Lymphadenopathy
- Iron deficiency anemia
- Thyroid enlargement (thyromegaly)
- Increased hepatic transaminases
- Muscular atrophy (noted in some subjects)

11.2 Hypoglycemia management

Hypoglycemia is the dose-limiting toxicity of all IGF-1 axis therapeutics. Glucose monitoring should be performed at treatment initiation, upon dose increases, and when symptoms occur. Severe hypoglycemia (requiring external assistance or loss of consciousness) occurred in a minority of subjects. Risk mitigation includes ensuring adequate caloric intake, avoiding administration in fasting states, and maintaining a regular meal schedule. The lower hypoglycemic incidence relative to free rhIGF-1 represents the principal safety advantage conferred by the IGFBP-3 component [1, 11].

11.3 Intracranial hypertension

Papilledema (suggesting elevated intracranial pressure or pseudotumor cerebri) has been reported with both mecasermin and mecasermin rinfabate. Fundoscopic examination should be performed at baseline and periodically during treatment. If

papilledema is confirmed, treatment should be interrupted until resolution [1].

11.4 Potential oncogenic risk

IGF-1 receptor signaling promotes cellular proliferation and inhibits apoptosis; epidemiological data associate elevated circulating IGF-1 levels with increased risk of certain cancers (breast, prostate, colorectal). The theoretical oncogenic risk of chronic IGF-1 axis stimulation is a class concern for all IGF-1 therapeutics. No malignancies were reported in the limited clinical development program, but long-term safety surveillance was not conducted [1, 16].

11.5 Ovarian cysts

Ovarian cysts were reported in female subjects during treatment, consistent with the known effect of IGF-1 on ovarian follicular development and steroidogenesis [1].

11.6 Limitations of safety data

Safety data beyond one year of continuous treatment are limited, and safety beyond 21 months has not been established. The small size of the clinical development program (36 subjects in the pivotal cohorts), the brief commercial availability, and the absence of long-term post-marketing surveillance data represent significant limitations in the safety characterization of mecasermin rinfabate [1].

11.7 Neonatal safety

In the Phase 2 preterm infant trial, the safety profile of continuous intravenous rhIGF-1/rhIGFBP-3 was generally acceptable, with no unexpected serious adverse events attributed to the study drug. Hypoglycemia management in this population requires continuous glucose monitoring given the metabolic instability inherent to extreme prematurity [15].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five IGF-1 axis therapeutics and related growth-promoting compounds against mecasermin rinfabate, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation.

12.1 Mecasermin (Increlex; free rhIGF-1)

Mechanism: Direct IGF-1 receptor agonism via unbound recombinant human IGF-1 (70 amino acids, 7,649 Da). Identical receptor pharmacology to the IGF-1 component of mecasermin rinfabate but without the pharmacokinetic modulation provided by IGFBP-3 [30].

Development trajectory: Developed by Tercica (now Ipsen), approved by the FDA in August 2005 for severe primary IGF-1 deficiency. Remains the only currently marketed IGF-1 replacement therapy. Administered twice daily by subcutaneous injection at 0.04 to 0.12 mg/kg per dose [30].

Novelty: Low. The mechanism is direct receptor agonism with the endogenous ligand; no pharmacological novelty beyond recombinant production.

Effect size: Comparable to mecasermin rinfabate in promoting linear growth in primary IGFD. First-year height velocity increases of 5 to 8 cm/year from baselines of 2 to 4 cm/year are reported in published long-term follow-up studies [30, 31].

Promising potential: Moderate. Remains the standard of care for severe primary IGFD as the only commercially available product. Clinical development continues for additional indications. The compound is currently marketed.

Side-effect profile: Higher incidence of hypoglycemia (42 percent) compared to mecasermin rinfabate (31 percent). Requires twice-daily injection. Intracranial hypertension, tonsillar hypertrophy, and lymphoid tissue growth are reported [30].

Overall validation: High. Longest clinical experience of any IGF-1 replacement therapy with published long-term follow-up extending beyond 10 years in some cohorts [31].

Comparison to mecasermin rinfabate: Mecasermin (Increlex) has the advantage of current commercial availability, longer clinical follow-up, and continued FDA approval. Mecasermin rinfabate had the advantages of once-daily dosing, lower hypoglycemic incidence, and more physiological pharmacokinetics mimicking the natural binary complex, but these advantages became moot upon market withdrawal.

12.2 Somatropin (recombinant human growth hormone)

Mechanism: Growth hormone receptor agonism stimulating hepatic IGF-1 production, direct growth plate effects, and lipolysis. Operates upstream of IGF-1 in the somatotrophic axis [32].

Development trajectory: Multiple manufacturers. Approved for numerous indications including growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age, and idiopathic short stature. Not effective in patients with GH insensitivity (the mecasermin rinfabate population) [32].

Novelty: Low. The mechanism is physiological hormone replacement; the compound has been in clinical use since the 1980s.

Effect size: Large in GH-deficient patients (height velocity increases of 8 to 12 cm/year in the first year). Ineffective in GH-insensitive patients who represent the target population for mecasermin rinfabate.

Promising potential: High for GH-responsive conditions. Not applicable to GH-insensitive conditions.

Side-effect profile: Generally well tolerated. Fluid retention, arthralgia, carpal tunnel syndrome, and theoretical oncogenic risk. Lower hypoglycemic risk than IGF-1 therapeutics.

Overall validation: Very high. Decades of clinical experience, extensive long-term safety data, and multiple large-scale registries.

Comparison to mecasermin rinfabate: The compounds target different patient populations with no therapeutic overlap. Somatropin cannot treat GH-insensitive patients; mecasermin rinfabate cannot add value in GH-deficient patients with intact receptor function. They are mechanistically complementary rather than competitive.

12.3 Lonapegsomatropin (TransCon hGH)

Mechanism: Long-acting growth hormone receptor agonism via a prodrug consisting of somatropin transiently conjugated to a polyethylene glycol carrier through a TransCon linker that releases unmodified somatropin with a half-life of approximately one week, enabling once-weekly injection [33].

Novelty: Moderate. The mechanism is conventional GH receptor agonism; the novelty is the extended-release delivery technology.

Effect size: Non-inferior to daily somatropin in pediatric GH deficiency (height velocity approximately 11 cm/year in year 1). Not effective in GH-insensitive patients [33].

Promising potential: High for GH-responsive conditions. Approved (Skytrofa) in 2021 for pediatric GH deficiency. Not applicable to IGFD.

Side-effect profile: Similar to daily somatropin with lower injection burden.

Overall validation: High within its approved indication. Growing clinical experience.

Comparison to mecasermin rinfabate: Same non-overlap as somatropin. Lonapegsomatropin addresses the convenience limitation of daily GH injection but does not extend to GH-insensitive populations.

12.4 Tesamorelin (growth hormone releasing factor analog)

Mechanism: Growth hormone releasing hormone (GHRH) receptor agonism stimulating pituitary GH secretion. Operates upstream of both GH and IGF-1 [34].

Novelty: Moderate. Synthetic GHRH analog with improved stability.

Effect size: Approved for HIV-associated lipodystrophy at 2 mg daily subcutaneous injection, producing reduction in visceral adipose tissue. Not studied in IGFD or growth failure.

Promising potential: Limited to metabolic indications. Not applicable to GH-insensitive conditions.

Side-effect profile: Injection site reactions, arthralgia, peripheral edema. No significant hypoglycemic risk.

Overall validation: Moderate. Approved for a single metabolic indication with limited extension.

Comparison to mecasermin rinfabate: Mechanistically distinct (operates upstream of GH). Cannot treat GH-insensitive or GH-deficient conditions directly. Represents a different approach to somatotrophic axis modulation.

12.5 Pasireotide (somatostatin receptor ligand, comparative context)

Mechanism: Somatostatin receptor subtypes 1, 2, 3, and 5 agonism suppressing GH and IGF-1 secretion. Used therapeutically to reduce GH/IGF-1 excess in acromegaly; included as a mechanistic comparator representing IGF-1 axis suppression rather than augmentation [35].

Novelty: Moderate. Broader somatostatin receptor binding profile than octreotide.

Effect size: Produces significant suppression of IGF-1 levels in acromegaly. Mechanistically opposite to mecasermin rinfabate.

Promising potential: Not applicable to IGFD (would worsen the condition). Included to illustrate the bidirectional pharmacology of the IGF-1 axis.

Side-effect profile: Hyperglycemia (the inverse of the mecasermin rinfabate hypoglycemic signal), cholelithiasis, gastrointestinal effects.

Overall validation: High within acromegaly indication.

Comparison to mecasermin rinfabate: Mechanistically opposite. The hyperglycemic adverse effect of pasireotide (from IGF-1 suppression) mirrors the hypoglycemic effect of mecasermin rinfabate (from IGF-1 augmentation), illustrating the

dose-limiting toxicity at each extreme of IGF-1 axis modulation.

12.6 Comparator summary

Among compounds that augment IGF-1 signaling for growth-promoting or anabolic purposes, mecasermin rinfabate occupies a unique but currently inaccessible position. It offered pharmacokinetic advantages over free mecasermin (once-daily dosing, lower hypoglycemia) by replicating the physiological binary complex, but these advantages were neutralized by patent litigation and market withdrawal. Mecasermin (Increlex) remains the only available direct IGF-1 replacement. Somatropin and its long-acting formulations address GH-responsive conditions but cannot serve GH-insensitive patients. The principal unmet need in the mecasermin rinfabate patient population (severe primary IGFD) is a commercially available, once-daily, reduced-hypoglycemia IGF-1 replacement; this need remains unaddressed as of the current monograph revision.

The neonatal application (rhIGF-1/rhIGFBP-3 for prematurity complications) represents the most active current development of the mechanism, with no direct comparator among marketed therapeutics. The concept of physiological IGF-1 axis reconstitution in extremely preterm infants is novel and has produced Phase 2 efficacy signals that warrant continued development.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Mecasermin rinfabate (iPLEX) is no longer commercially available. The compound received FDA approval in December 2005 (NDA 021884) but was withdrawn from the United States market in March 2007 following patent litigation settlement. Investigators seeking access to the rhIGF-1/rhIGFBP-3 complex for research purposes must prepare the complex from individual recombinant components or access clinical-grade material through active clinical trial frameworks under successor sponsors. The safety database for mecasermin rinfabate is limited; long-term safety beyond 21 months of treatment has not been established.