SCIENTIFIC DISCUSSION

1. Introduction

Primary IGFD or Laron syndrome results typically from a defect in the growth hormone receptor (GHR). Dysfunction of GHR is characterized by clinical hyposomatotropism manifest by short stature, delayed bone age, and occasionally blue sclerae and hip degeneration. Additional features include delayed bone maturation and the absence of bone dysplasias and chronic diseases. Laron syndrome patients have low IGF1 despite normal or increased levels of GH. The GH is functionally normal by the criteria that it reacts normally with a variety of antisera and binds normally to GH receptors. IGF-1 is low in GHIS, and exogenous GH does not induce an IGF-1 response or restore normal growth. Plasma levels of GH-binding proteins (GHBP), which are derived from the extracellular domain of GHR, are often low.

INCRELEX (mecasermin) is recombinant human insulin-like growth factor-1 (rhIGF-1) designed for use as replacement therapy in severe primary insulin-like growth factor deficiency. Studies about its use in IGFD date back to 1989 and its efficacy has been proven also by the scientific literature.

The term of "Primary IGF-1 Deficiency" for this disorder was proposed by Z. Laron to distinguish between disorders in which a defect in GH action leads to IGF-1 deficiency and its associated effects on statural growth, compared to "secondary IGFD" which is caused by abnormalities in the GH/IGF-1 axis such as GH deficiency.

There are currently no products authorised in the European Union to treat patients affected by the condition. Recombinant human IGF-I, though not authorised, has been used for the treatment of patients with growth hormone insensitivity syndrome and primary IGF-I deficiency due to an IGF-I gene defect.

The application for INCRELEX according to Article 8.3.(i), is a complete application for a new active substance within the centralised procedure.

The proposed indication for INCRELEX was for the long-term treatment of growth failure in children with severe primary IGD-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralising antibodies to GH.

Mecasermin was granted orphan status in the EU for "Treatment of growth hormone insensitivity syndrome" (EU/3/05/307) on 26 August 2005.

In December 2005, in parallel to the marketing authorisation application, the sponsor submitted another application for orphan designation for "Long-term treatment of growth failure in children with primary insulin-like growth factor-1 deficiency (Primary IGFD)". On the 05 April 2006 the application was granted a positive opinion. It was considered that for the purpose of orphan designation the condition should be described as "primary insulin-like growth factor-1 deficiency due to molecular or genetic defects". The prevalence of the condition was established as affecting not more than 2 in 10,000 persons in the Community when the application was made, being the condition chronically debilitating due, in particular, to growth failure and dysmorphic features. Orphan status in the EU for this indication (EU/3/06/373) was granted on 22 May 2006.

2. Quality aspects

Introduction

Tercica Europe Ltd. has filed an application for marketing authorisation for INCRELEX (INN: mecasermin). INCRELEX is a medicinal product supplied as a sterile solution for the treatment of children with severe Primary insulin-like growth factor-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion, who have developed neutralizing antibodies to GH. The product is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05M acetate at a pH of approximately 5.4. The product is supplied as a sterile solution in 5 mL multiple dose glass vials (40 mg/vial).

The active substance of INCRELEX is recombinant human Insulin-like Growth Factor-1 (rhIGF-1), a single-chain, non-glycosylated polypeptide, composed of 70 amino acids. Its structure is stabilized with 3 intra-chain disulphide bonds.

rhIGF-1 is a 7.6 kDa peptide structurally identical to naturally occuring human IGF-1. It is highly homologous (45-52 %) with human insulin and has 67 % sequence identity with human IGF-2. Synthesis and release of natural occurring IGF-1 and IGF-2 is induced by human growth hormone (GH), whereas most of the growth-promoting effects of human growth hormone are mediated through IGF-1. In target tissues IGF-1 has one specific receptor, IGFR1, and in blood circulation IGF-1 is bound to carrier proteins called Insulin-like Growth Factor Binding Proteins (IGFBPs), from which IGFBP3 is the most important carrier for IGF-1.

Composition:

Component	Function	Quantity per mL	Quantity per Vial	Reference to Quality Standard
rhIGF-1	Drug Substance	10.0 mg	42.5 mg	In-house Specification
Sodium Chloride	Tonicity modifier	5.84 mg	24.8 mg	USP/Ph. Eur.
Glacial Acetic Acid	Buffer	0.43 mg	1.8 mg	USP/Ph. Eur.
Sodium Acetate, Trihydrate	Buffer	5.82 mg	24.7 mg	USP/Ph. Eur.
Polysorbate 20	Stabilizer	2.0 mg	8.5 mg	USP/NF/Ph. Eur.
Benzyl Alcohol	Preservative	9.0 mg	38.3 mg	NF/Ph. Eur.
Water for Injection	Solvent	qs to 1.0 mL	qs to 4.25 mL	USP/Ph. Eur.

Drug Substance

General Information

INCRELEX (mecasermin) is a recombinant human IGF-1, produced in *E.coli* bacteria. The biological activity of rhIGF-1 is based on its ability to stimulate cell growth both in vitro and in vivo.

Nomenclature

INCRELEX (mecasermin [rDNA origin] injection) is the trade name for the proposed recombinant human insulin-like growth factor-1 (rhIGF-1). The International Nonproprietary Name (INN) is mecasermin, CAS registry number 68562-41-4. The molecule is also referred to as IGF-1, human IGF-1 or as Somatomedin C.

Structure

Mecasermin is a basic, single-chain, non-glycosylated 70 amino acid protein connected via three disulphide bonds. The amino acid sequence of mecasermin is identical to the native IGF-1 as described in the literature.

Manufacture

Cambrex Bio Sciences Baltimore, Inc., 5901 East Lombard Street, Baltimore Maryland 21224, USA. is responsible for the manufacture of the Drug Substance, bulk Drug Product formulation and part of the Bulk Product release testing.

Development genetics

Cell source

The transcriptional and translational initiation sequences required for the expression of the IGF-1 gene in *E. coli* are provided by the Applicant. The nucleotide and amino acid sequences encoding the signal sequence and the IGF-1 gene are presented.

Cell banking

The MCB was carefully tested for viability, microbial purity and identity. The expression plasmid content was examined for segregational and structural stability. All the test were satisfactory and the phenotypes of the host strain fit to the genotype and the DNA sequence of the expression cassette is identical to the original *E. coli* strain and expression plasmid respectively. A working cell bank was prepared and tested under similar conditions as the MCB. The WCB passed the tests and is apt for large scale fermentations.

Master Cell Bank

The original rhIGF-1 MCB was produced by Genentech. From this MCB, the currently used MCB was produced. Results from the MCB testing are described.

Working Cell Bank

A Working Cell Bank was produced from the MCB. Testing and qualification of the WCB was performed.

Manufacturing process of the drug substance:

The rhIGF-1 is initially produced and deposited in an inactive form in the periplasmic space of the bacterial cells. Protein recovery involves isolating crude rhIGF-1. The protein is then refolded, under controlled conditions, to obtain the biologically active form. The purification process, using column chromatography and ultrafiltration, removes process-related and product related impurities, as well as product variants, prior to final bulk drug substance formulation.

The Applicant has followed the critical operation parameters during the manufacture of multiple commercial scale batches and most of the presented values are well within the acceptance limits. Results from in-process testing from the same batches are also provided and they mainly comply with the specifications.

Process validation and/or evaluation

Each individual manufacturing step has been validated for execution, expected performance, robustness and impurity clearance. The validation campaign consisted of three consecutive full scale lots. Validation data of the chromatographic purification steps include results of the critical process parameters and in-process controls.

The presented process validation contained also removal of process and product-related impurities. The analysis of process-related impurities was performed from different purification steps and the final amount of each impurity was measured. The clearance of process-related impurities from the drug substance is also presented.

Product related impurities

Removal of product-related impurities along the purification process has been described. The current manufacturing process of the drug substance (Tercica) is well described and the chosen in-process controls are acceptable. The minor issues associated to the manufacturing process and its consistency, are mostly properly addressed by the Applicant and only two minor issues are retained as commitments. The presented process validation is considered acceptable. For chemical process-related

impurities the company has provided safety risk analysis using available toxicological information. The lack of data for chemical impurities regarding materials produced by different process variants is considered acceptably covered. The levels of the only product-related impurity are properly controlled during the manufacturing process.

Characterisation

The observed amino acid sequence of rhIGF-1 was identical to the amino acid sequence predicted by the DNA sequence. The complete amino acid sequence of the same rhIGF-1 lot was confirmed. Characterization studies were mainly performed with Tercica rhIGF-1, however, older material was included in some of the studies as part of the comparability testing. The company has put a lot of effort to further characterize the protein molecule with state-of-art methods. Product heterogeneity has been assessed by chromatographic methods. Product variants have been isolated and identified from Tercica lots, and most of them have been identified as active forms. The only variant regarded as an impurity, is the inactive misfolded form of rhIGF-1.

Post translational modifications

rhIGF-1 is a non-glycosylated protein produced in *E.coli* and thus most post-translational modifications are not expected to take place. The lack of modifications is supported by the results presented. Additionally, the company has provided supportive evidence of the correctly folded protein.

Physicochemical properties

The molecular mass of Tercica produced rhIGF-1 was confirmed. According to the result, the molecular mass of mecasermin is 7649 Da, which is in agreement with the theoretical, calculated mass of rhIGF-1 (7649.6 Da).

Biological properties

Potency: Bioassay. An in vitro cell based bioassay is used to evaluate potency during routine release and stability testing of rhIGF-1 formulated bulk drug substance.

An International Standard (NIBSC rhIGF-1) approved by WHO is used as reference material in the bioassay. The bioassay is an in vitro cell based assay developed to measure the bioactivity of rhIGF-1. A validation study has been performed, the parameters examined and results are presented. The Applicant has also validated the storage of the reference material and submitted the requested data. Thus the bioassay is considered acceptable for the intended use.

Process-related impurities

The rhIGF-1 drug substance manufacturing process contains several process– related impurities including cell substrates (*E. coli* proteins and DNA), fermentation and recovery media and process components, and downstream processing buffer components comprising a residual solvent and buffer salt. Details for each process-related impurity are provided and summary data analysis from clinical lots, primary stability lots, and conformance lots are given within the drug substance process validation section. Validation of contaminant removal during process validation and justification of the final bulk contaminant limits for ECP and DNA were based on results obtained by the use of validated analytical methods for all impurities tested.

Specification

The Applicant has provided description of the analytical tests used for In Process -testing and for process validation purposes. Specifications defined for the drug substance are considered acceptable.

Validation of Analytical procedures

Specifications defined for the drug substance are considered acceptable. The analytical procedures are state-of-art methods and most of them are properly validated for the intended use, except one procedure requiring further development and for which a follow-up measure has been identified

Batch analysis data is provided not only for the consistency lots, but also for the early development batches. Analysis of the Tercica batches with the proposed methodology provides assurance of acceptable batch consistency for the current manufacturing process.

Release and stability assays and tests used for process validation purposes have been validated according to ICH requirements. Validation of critical in-process assays has also been performed as appropriate for the intended use of the assays. Additionally, stress studies were performed to further demonstrate the validity of methods. Validation reports for all methods are provided.

Batch Analyses
Summaries have been provided for batches used in non-clinical evaluation and clinical trials, as well as the consistency lots conducted at full scale. The batches comply with the proposed specifications. The company used three reference materials in the characterization and release testing of rhIGF-1. Both the older reference materials and the new Tercica reference material have been extensively characterized.

Stability
The formulated drug substance bulk is stored at 2 to 8ºC and has a proposed shelf life of 12 months. The current drug substance stability program is ongoing and the company commits to continue the stability testing of these batches to the end of the shelf-life. Additionally the Applicant commits to retest all batches prior to filling until full stability data is available.

Drug Product

The drug product is a sterile liquid formulation containing a preservative, and is intended for multiple administrations. It is supplied in a single configuration of 40 mg at a strength of 10 mg/mL rhIGF-1, and is stored at 2 to 8°C.

The active ingredient of drug product is recombinant human IGF-1 produced in *E.coli*. The drug substance is manufactured as a formulated bulk, stored at 2 to 8°C and shipped for sterile filtration and aseptic filling.

The formulated bulk drug substance pooled, mixed, sterile-filtered and automatically filled into sterile vials through aseptic processing. The manufacturing process is adequately validated and the quality control of the drug product is acceptable. All excipients are compendial, non-novel excipients and are sourced from approved vendors. The drug product contains no excipients of human or animal origin. The container closure system used for immediate packaging of the drug product has been found suitable and compatible with the product.

Pharmaceutical Development
rhIGF-1 has always been formulated for use as a sterile parenteral (subcutaneous injection) product. The development process of the product vials is well described. The formulation development module consists of summary of formulations used in clinical development and overages and the physicochemical and biological properties. The manufacturing process development module consists of the older manufacturing process and the Tercica manufacturing process and the changes. The dossier contains detailed information about the formulation and manufacturing development as well as on the development of the container closure system, its integrity and extractables and leachables testing.Extractables testing concerning extraction conditions and limits has been provided. The microbiological attributes including the issue of preservatives and the container closure integrity are addressed.

Modifications have been implemented in the manufacturing processes used to formulate, sterilize, and aseptically fill INCRELEX. A summary of the different processes, manufacturing sites, and corresponding drug substance manufacturing processes is presented. All drug product lots of INCRELEX have been manufactured by sterilization of the formulated bulk via 0.2 µm filtration and subsequent filling into sterile vials via aseptic processing.

The current container closure system is well documented and putative leachables have been studied. INCRELEX (mecasermin injection) is a sterile solution containing 0.9% Benzyl Alcohol NF as a preservative. During drug product manufacturing, the formulated bulk drug substance is sterilized by filtration and filled into sterile vials under aseptic conditions. All aseptic operations have been

validated by media fills. All sterile components, including vials, stoppers, and product contact filling equipment, are sterilized by validated methods. Each lot of INCRELEX is tested for sterility by compendial methods.

Manufacture of the Product

The manufacture of INCRELEX is performed by Baxter Pharmaceutical Solutions (BPS). The BPS facility is a multiple-product contract manufacturing facility. All biologic products currently manufactured at the facility have dedicated (and/or single use) product contact equipment and parts. The manufacturing process flow is presented.

The autoclaves used for sterilization of tubing, needles, filter assemblies, primary packaging material (vials and closures) and the surge tank were validated for worst-case durable load conditions that included all applicable components. The studies used challenge biological indicators (spore forming bacteria) to evaluate the suitability of the sterilization cycle with worst-case loads.

The sterile filtration process was validated by microbial retention validation study for rhIGF-1 formulated bulk drug substance using Hydrophilic 0.2 μm Durapore Membrane Filters. A summary report of the validation is provided.

Vial filling and stoppering are conducted under aseptic conditions. Routine media fills are performed that are adequate in design to validate aseptic processing under normal established operating conditions (duration of aseptic operations, vial configuration, fill volume, batch size). Results from the most current media fills are provided in the dossier.

The process validation contained the appropriate evaluations and the validation data is provided. Release data is provided for commercial full-scale lots of drug product manufactured using the process described.

Excipients used in formulation of INCRELEX are Sodium Chloride, Sodium Acetate, Glacial Acetic Acid, Polysorbate 20, Benzyl Alcohol and WFI. Sodium chloride, sodium acetate, polysorbate 20, benzyl alcohol, glacial acetic acid, and water for injection are all tested per procedures described in the current revisions of the USP, NF, or Ph. Eur. Compendial analytical procedures used for excipient testing have been verified to be suitable under actual conditions of use. All INCRELEX excipients meet either USP, NF, or Ph. Eur. specifications, or are multi-compendial, ensuring that they meet stringent international standards for identity, quality, purity, and safety.

The rhIGF-1 Drug Product contains no excipients of human or animal origin.

Product Specification

The specifications for INCRELEX drug product are summarized. The Applicant has provided description of the analytical tests used for release testing, including the appropriate method validations. Specifications defined for the drug product are considered acceptable, and as follow-up measures the applicant has committed to further refine and submit specifications for several key test methods, including the bioassay.

As an exemption to the defined Drug Product release tests, the biological activity of the final product is determined by an HPLC method instead of the bioassay. The validation of the HPLC assay, including bridging of the HPLC assay with the bioassay, has been performed and a specification has been accepted. Additionally, Tercica has agreed to perform the bioassay as a Drug Product in process test.

Stability of the Product

Drug product lots are being monitored for stability at the proposed long-term refrigerated storage condition 2-8°C. In addition, accelerated stability testing is being conducted at 25°C ± 2°C/60% RH ± 5% RH. The stability program is intended to extend up to 60 months and vials in upright and inverted position are included in the program, as well as vials put on accelerated storage conditions (25 °C/60 % RH).

According to the results, the product is well preserved and no clear deterioration of the rhIGF-1 material can be observed. The statistical analysis is performed according to ICH Q1E. However, as the company does not have full stability data for 24 months, the Applicant committed to continue the long term studies through the proposed shelf life and to provide the data as soon as it is available.

The finished INCRELEX drug product was also tested for stability over its period of intended use by the patient as each vial of product contains multiple doses. The in-use stability study encompassed a 30-day period in which the product was stored at 2-8°C and sampled multiple times in order to simulate typical handling while in use. A 30-day in use shelf life is proposed from the time of initial penetration and will be indicated on the product label.

Adventitious Agents
There is no risk of viral contamination from the production cell line, as this bacterial cell line, unlike mammalian host cell lines, does not support the replication of mammalian viruses that might be introduced during the cell growth and fermentation phases from raw or starting materials.

The rhIGF-1 manufacturing process contains one starting material and one raw material that are derived from animal sources. Details of each of these animal-sourced materials, including their origins, categorical risk assessments, manufacturing controls and other manufacturing information relative to the rhIGF-1 production process were provided. It is concluded that the use of the two materials derived from animal sources does not affect the safety of INCRELEX.

GMP
Satisfactory compliance with GMP has been demonstrated for:
-the manufacturer of the active substance Cambrex Bio Science Baltimore Inc, USA.
-the manufacturer of the medicinal product Baxter Pharmaceutical Solutions LLC, USA.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The Applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

The non-clinical programme consisting of pharmacology, ADME/toxicokinetics and toxicology studies was performed. Data from the literature supporting the use of rhIGF-1 at doses of 0.080 to 0.120 mg/kg given twice daily as subcutaneous (SC) replacement therapy for growth failure in children with primary IGFD was also submitted. The published literature was searched from 1966 to September 2004 using the National Library of Medicine database. Selected relevant references describing the use of rhIGF-1 produced by others were submitted.

All of the pivotal toxicological studies and toxicokinetic studies were conducted according to GLP guidelines. Considering types of preclinical models used to examine mechanism of action of mecasermin as well as relevant guidelines for biotechnologically derived drugs, deviations from GLP in some ADME and secondary pharmacology studies can be accepted.

Several early development formulations of mecasermin were used in different studies.

Pharmacology

- Primary pharmacodynamics

IGF-1 is a 7.649 kDa non-glycosylated protein of 70 amino acids with three intra-molecular disulfide bridges and is structurally homologous to proinsulin. IGF-1 is a mediator of statural growth (somatomedin) and it is obligate for GH to be able to stimulate bone and body growth. In target tissues the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by the binding of rhIGF-1 leading to intracellular signalling which stimulates multiple processes leading to statural growth, as well as mitogenic and "insulin-like" metabolic activities. The hypoglycaemic effect of IGF-1 is the most frequent adverse reaction observed during the clinical studies in primary IGFD. Insulin and IGF-1 stimulate glucose uptake in muscle in a qualitatively similar manner, but quantitatively the hypoglycaemic potency of IGF-1 is ≤ 10% of that of insulin in animals and humans. Low doses of rhIGF-1 have been reported to restore bone and body growth without exerting a glucose-lowering effect in diabetic rats.

Non-clinical pharmacology studies to characterize the pharmacodynamic (PD) effects of mecasermin included examination of metabolic and tissue growth responses. The pharmacological activity of mecasermin observed in all laboratory species (mice, rat, rabbit, rhesus monkey) examined are consistent with the fact that the amino acid sequence of IGF-1 and IGF receptors are highly conserved among species.

The primary pharmacodynamic endpoint, bone growth, was evaluated in two different GH and IGF-1 deficient rat models; the hypophysectomized rat and the dwarf (dw/dw) rat. Additionally, the ovarectomized rat was used as a model of bone loss and growth retardation. These animal models can be considered to be relevant enough and predictive of the bone growth response that was seen in human clinical trials of mecasermin treatment of children with primary IGFD. In all of these studies, mecasermin was administered as a continuous SC infusion. The reasons for using this route and mode of administration instead of SC bolus injection (widely used, no evidence for qualitative differences between injections and infusions, and minimization of hypoglycaemic effect) were reviewed and considered acceptable for evaluation of the primary pharmacodynamic endpoint, bone growth. The effect of mecasermin on bone growth was measured using three methods depending on the study: measuring the absolute length of the tibia, measuring the width of the epiphyseal growth plate, and determining the amount of new calcified bone formed between the oxytetracycline marker and the cellular growth plate in the tibia. A dose-related increase in bone growth was seen in all studies after 7 to 14 days of mecasermin SC infusion.

- Secondary pharmacodynamics

To determine the secondary PD effects of mecasermin on blood glucose, body weight gain and immune function, several studies in mice, rat, rabbit, and monkey were performed. In addition, the changes in weight of various organs were monitored in several pharmacology studies (see Toxicology section). All doses 1.0 mg/kg or greater and both routes of administration (SC bolus and intravenous (IV) bolus) caused a fall in the blood glucose levels in rats. The glucose response appeared to be greatest in animals with the lowest pre-dose glucose levels.

In most studies there was a dose-related effect of mecasermin on body weight gain. Mecasermin was shown to affect the immune system by inducing hypertrophic and hyperplasic effects on lymphoid organs (thymus and spleen). In addition direct effects on immune function were demonstrated.

- Safety pharmacology programme

No formal studies were performed regarding possible activity of mecasermin or the formulation components on known pharmacologic receptors.

In addition, no formal in vivo safety pharmacology studies were performed. Specific evaluations of cardiovascular and respiratory parameters (electrocardiography, blood pressure, respiration rate) were

performed however as part of the pivotal GLP repeat-dose toxicity studies in beagle dogs. This was considered acceptable as the effects of rhIGF-1 were similar to that of the referent insulin, and there are many literature references regarding the cardioprotective effects of the compound. It has to be considered that there is no relationship between the cardioprotective effect and QT interval prolongation.

The absence of CNS safety pharmacology studies was justified by the Applicant in view of the existence of very large literature on the effects of IGF-1 on the nervous system which rather than suggesting neurotoxicity, suggest that rhIGF-1 has overall a beneficial effect on the nervous system. Though this did not give any information on the neurotoxicity of the mecasermin in this application, it was considered that the safety aspects of IGF-I treatment were been sufficiently taken into account in the toxicological studies. The observed symptoms related to CNS in these studies were concluded to result mainly from the hypoglycaemic effect.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were performed with mecasermin and rhGH in mice, and normal, aged, hypophysectomized, and dwarf rats. Effects on bone growth, changes in blood glucose, changes in body weight, and immune function were evaluated when these two hormones were coadministered.

Pharmacokinetics

In biological fluids, mecasermin is highly bound (95% to 99%) to a family of IGF binding proteins (IGFBP 1-6) that play important roles in modulating pharmacokinetics and distribution, and hence its biological activity. Free IGF-1 is cleared more rapidly than IGF-1 bound to the endogenous binding proteins. In rats and dogs, the total IGF-1 generally increased proportionately with increasing dose, but the percent that was free increased greater than proportionately from a low of approximately 3% at 0.1 mg/kg/day to a high of approximately 73% at 10.0 mg/kg/day.

The species used in the ADME/toxicokinetic evaluations were normal adult Sprague Dawley rats (males and females, single and multiple SC and IV doses), New Zealand White rabbits (males, single IV and SC doses), Beagle dogs (males and females, multiple SC doses), and rhesus monkeys (males, single SC doses). Validated radioimmunossay (RIA) and associated methodologies to quantitate total and free IGF-1 in plasma were used for the pivotal toxicokinetic support studies and the majority of other studies.

Appropriate physicochemical in vitro and in vivo non-clinical and/or clinical studies were conducted to demonstrate that the material from each new process was comparable to the material from the previous process.

After SC doses as high as 10.0 mg/kg/day, mecasermin was relatively quickly absorbed. The SC bioavailability for total and free IGF-1 was 38 to 57% in rats and rabbits. The mean Cmax and AUC for total and free IGF-1 overall increased with increasing dose, less than dose proportionally for total IGF-1 and greater than or approximately equal to dose proportionally for free IGF-1. The mean half-life values for total IGF-1 decreased with increasing dose. The mean free IGF-1 t1/2 overall did not show consistent changes with increasing dose. The data in rats suggested absorption rate limited kinetics.

One single dose tissue distribution study was conducted in male rats after IV administration of ^{125}I-labeled rhIGF-1 at 10, 60, 200, and 400 minutes post-dose for tracer only and at 60 minutes for tracer plus excess unlabeled rhIGF-1 was examined after a radiolabeled tracer-only dose and after a radiolabeled tracer dose plus an excess of unlabeled mecasermin. The organs/tissues examined included adrenal, bladder (empty), blood, bone, brain, fat, heart, injection site, kidney, large intestine, liver, lung, muscle, pituitary, plasma, reproductive tract, skin, small intestine, snout, spleen, stomach, thymus and thyroid. The volume of distribution of IGF-1 was relatively small, likely due to its high protein binding. Radioactivity was distributed primarily to highly perfused organs, and/or possible

organs of elimination/action (kidney and liver) for up to 200 minutes post-dose. The brain showed negligible accumulation of radioactivity.

Two metabolism studies were conducted in male and female Sprague Dawley rats after IV administration of ^{125}I-labeled mecasermin. A large percentage of the plasma radioactivity (76-80%) was associated with intact protein for up to 210 minutes. Relative clearance differed for free ^{125}I-mecasermin and radioactivity associated with the binding protein complexes. Radioactivity associated with the high molecular weight binding protein complex cleared slowly (0.5 to 10 mL/min/kg), radioactivity associated with the low molecular weight binding protein complex was intermediate in clearance (16 to 48 mL/min/kg), and free ^{125}I-mecasermin was cleared most rapidly (168 to 204 mL/min/kg). The expected consequence of metabolism of therapeutic proteins is the degradation to small peptides and individual amino acids. Some of the degradation products of IGF-1, like Des(1-3) IGF-1, may be active.

Literature reports submitted by the Applicant supporting their claim that the capability for degradation of IGF-1 exists in the liver, as in many other cell/tissue-types were reviewed and considered acceptable.

Urinary, biliary, or faecal excretion studies were not conducted for mecasermin. Excretion in milk studies were not conducted for mecasermin, as such the SPC states that "Breastfeeding while taking INCRELEX is not recommended." Pharmacokinetic drug interaction studies, like induction or inhibition of drug metabolizing enzymes, were not performed.

Toxicology

Toxicological studies were conducted in normal laboratory animals and did not investigate toxicity of mecasermin in situations reflecting the clinical situation in children with primary IGF-1 deficiency (low blood IGF-1 levels) with normal (or elevated) GH levels.

- Single dose toxicity

A series of single dose SC and IV toxicology studies were performed in CD-1 mice, Sprague Dawley rats, New Zealand White rabbits, Beagle dogs, and Rhesus monkeys. The primary findings from these studies were anticipated reductions in serum glucose and clinical manifestations associated with profound hypoglycaemia seen at higher dose levels. In the rat and dog GLP single dose toxicology studies, hypoglycaemic responses were exacerbated by the animals being fasted overnight prior to dosing and deaths occurring. As expected for single dose studies, no evidence of anti-IGF-1 antibody formation was noted.

- Repeat dose toxicity

Repeat Dose Subcutaneous Studies in Sprague Dawley Rats

Four repeat dose SC toxicology studies were performed in rats. The results were consistent with the known and expected pharmacological effects of mecasermin. In these studies animals were fasted the night prior to the postdose serum glucose measurements.

In a 4-week study with, rats were dosed with 0 (vehicle), 0.2, 0.6, or 2.0 mg/kg/day by daily SC injection. Body weight gain was increased and there were transient alterations in haematology and clinical chemistry parameters. These effects, generally attributable to the pharmacological effects of mecasermin, were observed most notably at doses $\geq$ 0.6 mg/kg/day. The most dramatic effect noted was hypoglycaemia.

There were no gross or microscopic changes except for an increased incidence of extramedullary haematopoiesis in the liver and spleen, which was not judged to be adverse, and all changes were generally reversible after a 4-week recovery period.

A second 4-week study gave results consistent with the first SC study. Daily SC injections resulted in increases in body weight and similar changes in haematology and clinical chemistry parameters. Hypoglycaemia was seen at doses ≥ 0.3 mg/kg/day. At a dose of 1.0 mg/kg/day at Week 4, glucose values in males and females were 65% and 30% of controls, respectively. There were no anatomical pathology changes and all clinical changes were reversible.

In a 26-week SC study rats were dosed daily with 0 (vehicle), 0.25, 1.0, or 4.0 mg/kg/day. All doses resulted in increases in body weight and increases in absolute or relative weight of the salivary glands and lungs. At a dose of 4.0 mg/kg/day urinalysis changes were noted. In blood clinical chemistry alterations consisted of decreases in serum glucose and β-globulin (males only). Histopathology revealed increased cortical area of the thymus in high-dose males. In rats dosed with 4.0 mg/kg/day, following a 5-week treatment-free recovery, increases in body weight, increases in food consumption, alterations in selected clinical pathology parameters, and increases in weights of some organs (heart, lung, liver, kidneys, thymus, adrenal gland (females) were still present, and histopathology revealed decreased cortex area in the thymus of 1 out of 6 high-dose males and decreased thymic weight. On the basis of anatomical pathology and/or clinical pathology findings noted in 4.0 mg/kg/day rats, the No-Observed-Adverse-Effect-Level (NOAEL) for this study was determined to be 1.0 mg/kg/day.

Repeat Dose Intravenous Studies in Sprague Dawley Rats

Three repeat dose IV studies were performed in rats. In a 10-day study performed to define dose levels in a subsequent 4-week study, mecasermin was administered at doses of 0 (vehicle) or 1.0 mg/kg/day. The only mecasermin-related effects noted were significant reductions in serum glucose 15 to 30 minutes following administration. In the rat IV studies, as in the rat SC studies, serum glucose and clinical pathology determinations were conducted in fasted animals.

In a 4-week study, mecasermin derived from the fusion process was administered daily at doses of 0 (vehicle), 0.05, 0.25, or 1.0 mg/kg. Mecasermin-related effects were confined to effects upon clinical pathology and an increase in heart weight (≥ 0.25 mg/kg/day females). The most significant clinical pathology changes consisted of reductions in serum glucose and inorganic phosphorus.

In a 13-week study, mecasermin was administered daily at doses of 0 (vehicle), 0.25, 1.0 or 4.0 mg/kg and was well tolerated at doses up to 4.0 mg/kg/day. Aside from anticipated dose-related increases in body weight and food consumption, an increase in serum phosphorus (considered to be a rebound effect from the prior day's dose) and transient increases in urinary sodium, potassium (statistically significant in males), and chloride excretion and increases in urine volume were observed in 4.0 mg/kg/day treated males and/or females. Following a 5-week recovery period, the absolute (but not relative) weights of several tissues (thyroid, thymus, heart, lungs, liver, kidneys, and adrenal gland) were increased in females treated with 4.0 mg/kg/day. There were no mecasermin-related microscopic findings noted in this study.

Repeat Dose Subcutaneous Studies in Beagle Dogs

Two repeat dose SC toxicology studies were performed in dogs. In a 4-week study with mecasermin derived from the ds process dogs were dosed daily at doses of 0 (vehicle), 0.1, 0.3, or 1.0 mg/kg. Doses of 0.1 and 0.3 mg/kg/day resulted in decreases in eosinophils, serum cholesterol (slight and not biologically significant) and, as expected, serum glucose. All animals in the 1.0 mg/kg/day group were sacrificed moribund due to apparent hypoglycaemic-induced convulsions during the first week of the study (Day 6). The condition of these animals was likely to be the result of an overnight fast.

In a 26-week study with mecasermin, dogs were dosed daily at doses of 0 (vehicle), 0.15, 0.3, or 0.6 mg/kg. Body weight tended to be higher in dogs receiving mecasermin. Serum glucose was reduced in all groups dosed with mecasermin. Serum potassium and phosphorus levels were decreased post-dose across all dose groups tested whereas pre-dose phosphorus levels were increased. At the cessation of treatment, increases in absolute or relative weights of adrenal, thymus, heart, submandibular gland, and pituitary tissues were observed. Microscopic findings in animals that survived until the scheduled sacrifice consisted of adrenal medullary hyperplasia and fibrosis at doses ≥ 0.3 mg/kg/day. For this

study, the NOAEL was determined to be 0.15 mg/kg/day. Full recovery was evident from doses of 0.3 mg/kg.

Repeat Dose Intravenous Studies in Beagle Dogs

Three repeat dose IV toxicology studies were performed in dogs. In these studies, dogs were fasted overnight prior to the collection of blood for glucose and clinical pathology analyses. In a 10-day study performed with mecasermin derived from the fusion process, dogs were dosed daily at 0 (vehicle) or 0.5 mg/kg. Transient clinical signs consistent with hypoglycaemia occurred sporadically. Hypo-activity was also noted 2 to 4 hours following the first administration. An increase in body weight gain and transient reductions in serum glucose were also observed in mecasermin treated dogs.

In a 4-week study with mecasermin, dogs were dosed daily at doses of 0 (vehicle), 0.025, 0.125 or 0.5 mg/kg. Ocular discharge and increased body weight and/or body weight gain and food intake were observed most notably at doses ≥ 0.125 mg/kg/day. Observations consistent with hypoglycaemia were seen at a dose of 0.5 mg/kg/day. No mortalities occurred. Clinical pathology changes included: lower absolute eosinophil count at doses ≥ 0.125 mg/kg/day; dose-related reductions in serum glucose, phosphorus, and/or potassium levels. All changes exhibited evidence of reversibility and there were no mecasermin-related microscopic alterations.

In a 13-week study with mecasermin, dogs were dosed daily IV at doses of 0 (vehicle), 0.025, 0.125, or 0.5 mg/kg. In the high dose group two of five females died due to hypoglycaemia. Increases in body weight and body weight gain were seen at 0.5 mg/kg/day. Reductions in serum glucose, potassium and phosphorus and/or increases in chloride were noted across all dose groups. Increased adrenal weights were the only anatomical pathology findings noted in all treatment groups at the scheduled 13 weeks or after 5 weeks of recovery.

There was no detectable antibody formation to IGF-1 in the majority of multiple dose studies conducted in dogs.

- Genotoxicity

No evidence of genotoxicity was observed with mecasermin in an *in vitro* chromosomal aberration test conducted in Chinese hamster lung fibroblasts at concentrations up to 487 µg/mL. Concentrations that limited exposure were determined in previous cytotoxicity studies. No evidence of genotoxicity was observed in an *in vivo* mouse micronucleus test employing IV doses up to 97.4 mg/kg.

- Carcinogenicity

In a 2-year carcinogenicity study, rats were dosed daily SC at doses of 0 (vehicle), 0.25, 1.0, 4.0, or 10.0 mg/kg. Mortality was increased in a statistically significant manner at doses ≥ 1.0 and 4.0 mg/kg/day, respectively. Hypoglycaemia appeared to be a major contributor to death/moribundity. Conversely, a trend toward a reduction in mortality was observed in females at a dose of 0.25 mg/kg/day.

Benign proliferative lesions of the adrenal medulla (hyperplasia and/or benign pheochromocytoma) were each increased in males and females given doses ≥ 1.0 mg/kg/day. At 0.25 mg/kg/day, comparisons with concurrent controls showed that combined lesions of the adrenal medulla were elevated in females only. The pathology report cited that there was a dose-related increase in proliferative lesions of the adrenal medulla which was most evident in females and was significantly increased at all dose levels

Benign epithelial neoplasms of the skin (primarily keratocanthoma and squamous cell papilloma) were increased in a statistically significant manner in males given doses ≥ 4.0 mg/kg/day. The incidence of palpable masses (primarily in the mammary gland region) for females and males was also increased at doses of ≥ 4.0 mg/kg/day by the end of the study (Weeks 84 to 105). The overall incidence, multiplicity, and type of mammary gland neoplasms (fibroadenoma, carcinoma, and galactoceles)

were similar across all female dose groups. When adjusted for survival, a statistically significant increase in the incidence of mammary fibroadenomas (4.0 and 10.0 mg/kg/day) and carcinomas (10.0 mg/kg/day) was observed. Marginal increases in mammary gland carcinomas in males and possibly benign skin neoplasms in females were also seen at the 10.0 mg/kg/day dose level (due to their low rate of occurrence of these tumors, statistics were not performed as designated in the study protocol).

The increased incidence of selected spontaneous tumors commonly seen in Sprague Dawley rats in the carcinogenicity study could be related to a potential direct mitogenic or anti-apoptotic effect of mecasermin and/or indirect contributing factors including effects upon calcium metabolism, blood glucose, body weight, and food consumption. With regard to the benign adrenal medullary pheochromocytomas, their clinical relevance is uncertain based upon the marked differences in background tumor patterns between rats and humans, and the possible effects of altered calcium metabolism, repeated hypoglycaemic episodes, and increased food intake and body weight acting to increase the incidence of these lesions. An increased incidence of benign skin (definitively in males) and mammary neoplasms (when adjusted for survival, statistically significant in females) were noted at doses ≥ 4.0 mg/kg/day; the No-Observed-Effect-Level for these lesions was 1.0 mg/kg/day which represents a 3 to 6-fold multiple of the clinical exposure on an AUC basis.

The Applicant has calculated (based on the toxicokinetic findings in carcinogenicity study and repeat-dose toxicity study) that animal to human exposure ratios are between 0.5 and 10 depending whether Cmax- or AUC-values are used.

- Reproduction Toxicity

Three repeat dose fertility and developmental toxicology studies were performed. In a multi-week IV rat study, mecasermin was administered daily to male and female rats at doses of 0 (vehicle), 0.25, 1.0 or 4.0 mg/kg. There were no effects on the reproductive performance and no effects on the foetuses.

In another rat study, mecasermin was administered IV daily at doses of 0 (vehicle), 1.0 4.0 or 16.0 mg/kg to pregnant rats from days 7 through 17 of gestation. No test article related effects on foetuses or live-born pups were observed. In a developmental toxicity rabbit study, mecasermin was administered IV daily at doses of 0 (vehicle), 0.125, 0.5, or 2.0 mg/kg to pregnant rabbits from days 6 to 18 of gestation. At the high dose of 2.0 mg/kg there was a statistically significant increase in the number of resorbed/dead foetuses per number of implantations, but no teratogenic effects. Increases in this parameter at doses of 0.125 and 0.5 mg/kg were not statistically significant. The increase in resorptions/dead foetuses is not unexpected given the glucose lowering effects of mecasermin.

Although animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, these studies were conducted by the IV route (not the normal clinical route) and the results may not be relevant. However, taking into account the intended paediatric use of mecasermin, the insufficiency or lack of reproductive toxicity studies is approvable, provided that pregnancy is contraindicated. This is reflected in the SPC.

- Toxicokinetic data

Toxicokinetic and serum glucose analyses performed following the initiation and conclusion of the dosing period in all repeat dose toxicology studies indicated that exposure and pharmacological responsiveness to mecasermin was maintained in the repeat dose rat and dog studies throughout the intended duration of treatment. Increase in body weights and hypoglycaemic effects continued throughout the majority of rat studies, indicating there was no cross reactive antibody formation which interfered with responsiveness to the hormone. In the rat carcinogenicity study dosing for up to 104 weeks caused sustained effects on food intake, whole body growth, and acute hypoglycaemia. These maintained pharmacological effects also indicated that in the rat biologically significant antibodies against mecasermin are not generated during prolonged or life-time drug exposure.

- Local tolerance

Local tolerance studies performed in New Zealand White rabbits indicated no significant local toxicity following SC or IV application. Mecasermin also tested negative, *in vitro*, for haemolytic potential and plasma incompatibility in human and canine blood and plasma.

- Antigenicity and immunotoxicity

There was no detectable antibody formation to IGF-1 in the rat toxicology studies or in the vast majority of studies conducted in dogs. Barely detectable but positive antibody titers to IGF-1 were detected in 2 out of 12 dogs treated with 0.5 mg/kg/day and 2 out of 12 dogs treated with 0.125 mg/kg/day in the 4-week IV toxicology study confirming the ability of the assay utilized to measure anti-IGF-1 antibodies. There was no evidence of antibody-mediated toxicity in any rat or dog toxicology study.

Ecotoxicity/environmental risk assessment

In accordance with the Draft Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00) applicable at the time of submission, an Environmental Risk Assessment was not submitted for INCRELEX. Substances such as peptides and proteins can be exempted from testing because they are unlikely to result in significant exposure of the environment and will consequently be of low environmental risk. This is considered to be the case with INCRELEX where the active substance (mecasermin) is a recombinant human protein that is identical to the native human protein.

Discussion on the non-clinical aspects

No stand-alone safety pharmacology has been carried out in the preclinical program. The omission of selected types of stand-alone studies (safety pharmacology) typically performed with conventional pharmaceutical agents is not considered to be of major significance based upon the nature of the product, especially when cardiovascular/respiratory endpoints in the repeat dose dog studies, and the existing clinical symptomatology data are included. Nevertheless, when administered at single dose levels as required in safety pharmacology, drugs can actually exert effects qualitatively and qualitatively different from those produced after prolonged administration of toxic doses.

While potential exceptions from current regulatory guidance exist with respect to reproductive toxicology (studies were performed by the IV route instead of the proposed clinical route of SC administration, maternal toxicity not being achieved in rat and rabbit reproductive toxicology studies, selected endpoints omitted (i.e., sperm count/viability) and no prenatal or postnatal data obtained), these exceptions are thought to be not of critical importance relative to assessing the potential reproductive risks posed by mecasermin in the clinical population, which will be a paediatric population.

Although regulatory guidance recommends that as part of a standard battery of genotoxicity tests for conventional pharmaceuticals, a bacterial gene mutation assay be performed, it has been agreed that the range and type of genotoxicity studies routinely performed for conventional pharmaceuticals are not applicable for biotechnology derived products. Other regulatory guidance recommends an assessment of mitogenic and carcinogenic potential of insulin analogs. The indication for which approval is sought is whole body growth promotion, for which a compound needs to have mitogenic activity, so the mitogenicity assessment was not performed. However a life-time carcinogenicity study was performed which obviates the need for the mitogenicity test.

Given that a paediatric population will be receiving mecasermin, toxicology studies in young and/or IGF-1-deficient and IGFBP-3 deficient animals could provide additional information beyond that provided in the existing studies performed in young adult or normal adult animals. It is uncertain, however, whether such data would provide additional relevant information beyond that in the existing toxicology and clinical studies. While the age, stage of development, and physiology of the intended patient population may differ from the animals used in the toxicology studies, it is important to note that even in adult rats, the epiphyseal plates of the long bones remain open for the majority of the

lifespan, making the young adult rat a suitable animal model for assessing mecasermin's effects upon bone growth and related statural endpoints in a human paediatric population. This physiologic characteristic also explains the large size attained by the rats in the two year carcinogenicity study as they remained pharmacologically responsive to mecasermin during prolonged treatment throughout their mature lifespan.

Mecasermin is intended to be given to children for many years. During this time children may be affected by several, occasionally chronic diseases, with need for appropriate treatment. Consequently, the effect of mecasermin may potentially be influenced by several drugs. Though animal interactions studies would provide a relatively simple approach to this problem, no such studies with mecasermin, except the interaction study between rhIGF-1 and azathioprine, have been carried out.

4. Clinical aspects

Introduction

The application for INCRELEX according to Article 8.3.(i), is a complete application for a new active substance within the centralised procedure.

The clinical development program of was initiated by Genentech with studies in GH insensitivity syndrome. This development program was accepted by the FDA as a basis for a new drug application. During the course of the development, the indication of mecasermin treatment was extended for patients with type 1 and 2 diabetes mellitus, and cachexia of patients with HIV infection.

The pharmacokinetics of mecasermin was studied in healthy volunteers and diabetic patients (type 1 and type 2). One PK study in the target population was also submitted, however, due to limitations of this study the Applicant agreed to provide additional population PK data.

In 2002 Tercica acquired all rights and documentation related to mecasermin. To date, 4 safety and efficacy studies in children with IGF-1 have been completed and one study (1419) remains ongoing.

No scientific advice was sought or given during the development.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

During the development process of mecasermin studies have been conducted by sponsors other than the Applicant. Parts of the records referred to in this application are from those studies.

Five studies (F0206s, F0375g, F0632g, F0671g and 1419) have been conducted to evaluate the long-term safety and efficacy of mecasermin in children with severe Primary IGFD. These studies were conducted at 2 primary investigative sites in the United States in conjunction with multiple other sites worldwide, which were designated as sub-investigative sites under the primary U.S. sites.
Studies F0375g, F0632g, F0671g were conducted under a Genentech-sponsored U.S. Investigational New Drug Application (IND); study F0206s was conducted under Dr. Underwood's investigator-sponsored IND and monitored by Genentech. These studies were carried out in accordance with the relevant international research guidelines and requirements established by the principles described in the Declaration of Helsinki (and its amendments), the World Health Organization, and the U.S. Food and Drug Administration (FDA) under the standards of Good Clinical Practice (GCP) set forth by the International Committee on Harmonization (ICH).

Between 1990 and October 1998 Genentech was responsible for monitoring the studies. In 1998 Genentech discontinued the development program for mecasermin, and in October 1998, the continuation of the project was assumed by Dr. Louis Underwood at the University of North Carolina (UNC) under his IND. In October 2002 Tercica took over the responsibility for monitoring the studies.

Much of the clinical use of INCRELEX in the period between 1998 and 2002 seems to be from a "compassionate use" setting. It is acknowledged that the data taken from such settings can never equal in accuracy with those obtained in controlled clinical trials. However, the Applicant has shown reasonable efforts in collecting and confirming the data and has also committed to performing a number of post authorisation follow-up measures and specific obligations to further confirm the efficacy and safety of the product.

According to the Applicant, the pivotal PK-PD study MS302 was conducted in accordance with the ICH Guideline for Good Clinical Practice (ICH E6, 1996), with local regulatory and ethical requirements, and with the Declaration of Helsinki (version in force at the time of study initiation).

Pharmacokinetics

A total of 9 primarily pharmacokinetic (PK) studies were carried out with mecasermin, all except one with healthy volunteers. In F0188g there was also a small subgroup of diabetic patients, primarily type 1. Study MS302 was carried out to evaluate safety and PK-characteristics in patients with moderate or severe IGFD compared to healthy people. The table below describes the Pk ("F0" omitted for shortness). All subjects were healthy young adults (19 - 39 years) unless otherwise stated.

Study	Completed subjects	Design Group size	Product	Dose µg/kg	Route	Aim	Analyte Total, free	Main parameters
176g	24 M	X-over	Fs,ds	50	IV	Bioequiv.	T, F	AUC0-24 h, Cmax
580g	19 M, 13 F	X-over	Ds, ps, 1 K	80	SC	Bioequiv.	T	AUC0-72 h, Cmax
115g	6 + 11 M	3/group	Fs	10-100	IV	Dose escal.	T, F	AUC0-24 h, Cmax
152g	12 M	12	Fs	30 x 5	IV	Repeated	T, F	C0, Cmax
174	9 M	TPN	Ds	5-200	IV	Metab. eff.	Terminated before end	
183g	7 M, 3 F	Conc. Ster.	Ds	5-10	IV	Metab. eff.	Terminated before end	
188g	38 M, 19 F	Age,DM	Ds	10-40	IV	Metab. eff.	Terminated before end	
317g	6 + 6	6/gr	Ds	100-120 X 4	SC	Food eff.	T, F	AUC0-12 h, Cmax
MS302	17 M, 19 F	12/gr	Ps, 1K	15-120	SC	Dose linear.	T	AUC0-inf, Cmax

TPN = total parenteral nutrition was given concomitantly
Conc.ster. = concomitant steroid
DM = diabetes mellitus

Bioanalytical methods

In the only PK study (MS302) relevant to the product intended to be marketed (manufactured using ps process), total IGF-1 was measured using a competitive binding radioimmunoassay (RIA). The assay method was not documented to current bioanalytical standards and validation studies were not performed. No cross-reactivity studies (eg. to pro-insulin) are reported.

- Absorption

Mecasermin is a peptide which breaks down in the gastrointestinal (GI) tract; it has to be administered parenterally. Since it is an injectable product, absorption from the GI tract has not been studied

The bioavailability of mecasermin after SC administration in healthy subjects has been approximated to be 100%; that is, no significant metabolism of the peptide occurs at the site of injection.

- Distribution

Mecasermin is extensively (over 80%) bound to specific binding proteins in blood, especially to IGFBP-3 and an acid-labile subunit. These binding proteins are greatly reduced in subjects with severe Primary IGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects.

Since mecasermin is an endogenous peptide it is acknowledged that it may be impossible to determine V_D exactly in healthy people. No studies with labelled IGF-1 in human have been carried out. Hence, the application contained a variety of estimations of distribution volumes.
In subjects with severe Primary IGF-1 deficiency (IGFD), V_D can be more reliably determined since the endogenous levels of IGF-1 in blood are low. The apparent volume of distribution (mean ± sd.) of total IGF-1 after SC administration of mecasermin (dose of 0.045 mg/kg) manufactured by ps 1K process was estimated to be 0.26 (± 0.07) l/kg.

- Elimination

Both the liver and the kidney have been shown to metabolise IGF-1. The Applicant has not studied metabolism of IGF-1 in humans.

The average (SD) apparent terminal elimination rate of total IGF-1 varied between 20 and 30 hours after a single SC dose of mecasermin. Free IGF-1 in plasma has significantly shorter half-life compared to bound IGF-1. The mean T½ elim after 0.07 mg/kg IV dose was less than half an hour.

In severe IGFD elimination rate seems to be faster. After single SC administration of 0.12 mg/kg of mecasermin in paediatric patients with severe IGFD, The mean terminal T½ elim was estimated to be 5.8 hours (study MS302).

Since the free fraction of IGF-1 is eliminated much faster than the bound fraction, clearance of mecasermin is inversely proportional to IGFBP-3 levels. Systemic clearance (CL/F) is estimated to be 0.04 l/hr/kg at binding protein (IGFBP-3) level of 3 ug/ml.

- Special populations

Pharmacokinetics of mecasermin have been characterised in children with IGFD and in diabetic patients. Patients with IGF-deficiency (IGFD) had lower IGF-1 levels and seemed to have faster elimination rate of IGF-1. However, this may be due to the confounding effect of endogenous IGF-1 synthesis and release in healthy subjects; therefore the T½elim of IGF-1 in healthy may be estimated to be too long.

Diabetics tended to have lower IGF-1 levels before and after IV administration of ds IGF-1, independent of age.

In children with Primary IGFD and in healthy adults there were no apparent differences between males and females in the pharmacokinetics of mecasermin.

No studies have been conducted in children or adults with renal or hepatic impairment. Nor have the pharmacokinetics been studied in elderly subjects with age greater than 65 years. These points have been reflected in the SPC. All healthy volunteers in the PK and PD studies were lean, with a body mass index (BMI) < 27 kg/m2.

- Pharmacokinetic interaction studies

Pharmacokinetic interaction studies have not been performed in healthy volunteers or with patients.

- Pharmacokinetics using human biomaterials

Classical biotransformation studies are not needed for biotechnology products (ICH S6)

In conclusion, out of the 9 PK studies only two were performed with the product to be marketed (manufactured by periplasmic secretion process). Data of the earlier studies is considered as supportive. There is a lack of PK data in the target population, and the incomplete validation of the laboratory methods regarding the detection of rhIGF-1 antibodies and also the free IGF-1 in the serum of the trial subjects puts the whole documentation related to immunological safety and PK in the target

population under question. In order to address this lack of information the Applicant has committed to performing a real population PK study in the target children population as a post-authorisation commitment.

Pharmacodynamics

- Mechanism of action

IGF-1 mediates effects of growth hormone (GH). IGF-1 has two main actions: it promotes growth in bones, and has insulin-like action in many types of tissues and cells. The anabolic effects include stimulation of cellular uptake of glucose, fatty acids, and amino acids which support growth of tissues. IGF-1 also promotes growth in bones by stimulation of chondrocytes, and has direct mitogenic activity in many cells.

The insulin-like action includes suppression hepatic glucose production, stimulation of peripheral glucose uptake, and reduction of blood glucose. In addition, IGF-1 has inhibitory effects (direct and indirect via blood glucose level) on insulin secretion.

- Primary and Secondary pharmacology

Primary pharmacodynamics: No PD studies were designed specifically to correlate growth in children with severe IGFD to IGF-1 concentrations after administration of mecasermin.

Secondary pharmacodynamics: One clinical pharmacology study examined the relationship between plasma free IGF-1 and serum glucose concentrations. The study was prematurely terminated. In general, insulin levels in serum decreased following mecasermin administration.
Effects on carbohydrate metabolism were studied in all PK studies with healthy volunteers for safety purposes. In some studies serum insulin levels were also determined.

Overall, IGF-1 systematically decreased blood glucose levels. The effect was stronger after IV administration compared to SC administration, and was seen already after a bolus IV dose of 0.01 mg/kg. In healthy lean men the dose dependency to reduction of blood glucose was weakly positive.
After a single dose administration mecasermin acutely reduced serum GH levels in IGFD patients. It was followed by a rise in GH, likely due to a rebound in GH secretion. In healthy adolescents / adults the effect of a single mecasermin dose on GH levels was minimal, and no dose-dependency could be seen (Study MS302). Mecasermin administration also increased serum IGFBP-3 concentrations above baseline levels.

Single doses of IGF-1 did not produce systematic cardiovascular effects in the PK trials. Single SC doses of 0.1 – 0.12 mg/kg of mecasermin did not increase appetite significantly

Pharmacodynamic interaction potential: Two phase I clinical studies studying PD interactions of mecasermin and other medicines or substances were initiated, but all were prematurely terminated due to safety concerns related to mecasermin infused IV for longer periods.

In conclusion, PD data in mecasermin's documentation come primarily from safety measures only. PD on carbohydrate metabolism was to be studied in healthy adults and diabetic patients in F0188g, and protein metabolism in F0183g, however these studies were interrupted due to safety concerns about mecasermin IV infusion. No metabolic data of these studies is available.

Clinical efficacy

Five studies have been conducted to evaluate the long-term efficacy and safety of mecasermin in children with severe primary Primary IGFD, these can be seen in the table below which also includes safety study MS301.

Study	Number of Subjects	Doses Used	Process/ Formulation	Study Design
F0206s	8	80-120 µg/kg BID	ds/citrate	Open-label, Investigator sponsored
F0375g	8	80-120 µg/kg BID	ds/citrate	Double-blind placebo controlled, crossover
F0632g	6	60 µg/kg BID	ds/citrate	Open-label
F0671g	23	80-120 µg/kg BID	ps/acetate	Open-label Multi-center
1419 (ongoing)	76[a]	80-120 µg/kg BID	ps/acetate	Open-label, Multi-center Investigator sponsored
MS301 (ongoing)	10[b]	0, 40 µg/kg BID, 80 µg/kg BID	ps/acetate	Open-label, randomized, multi-center, observation-controlled, parallel-dose, comparison

[a] Data cutoff date is 07 April 2005 for study 1419.
[b] Data cutoff date is 05 April 2005 for study MS301.

Four studies have been completed: one phase II (F0206s) and three phase III (F0375g, F0632g, and F0671g) trials. A long-term, open-label, extension study (1419) is ongoing. All patients from the previous efficacy studies are included in this phase III integrated study, and all results from these studies are integrated into 1419.

A total of 76 subjects were enrolled in one or more of these studies and all subjects except one were enrolled in Study 1419. 67 of the 76 subjects were naïve to rhIGF-1 treatment. Twenty-two of the subjects enrolled in study 1419 were treated with mecasermin in one or more earlier studies.

- Dose response study

F0632g: A phase III open-label, multicenter study of rhIGF-I in naïve children with short stature due to growth hormone insensitivity syndrome (GHIS)

Objectives

To determine whether replacement therapy with mecasermin, at a dose of 60 µg/kg given BID by SC injection to children with severe Primary IGFD and naïve to mecasermin, was safe and effective in improving linear growth. This was performed to determine if a lower mecasermin dose than had been used previously could be efficacious.

Treatments

Subjects received open label mecasrmin at a dose of 60 µg/kg SC BID on Days 3, 4, and 5. If this dose was well-tolerated, the subject continued the dose for one year. If the dose was not tolerated (as exhibited primarily by hypoglycaemia), the subject was not eligible for participation in the study.

In this study 6 naïve-to treatment subjects including 1 placebo group subject from study F0375g, enrolled and received mecasermin 60 µg/kg BID for one year.

Outcomes/endpoints

The primary efficacy measure was linear growth rate. The secondary efficacy measure was change in standardised height.

Safety was assessed by report of adverse events, physical examination, review of clinical laboratory evaluations including serum chemistry, haematology and urinalysis, antibodies to IGF-1, and reports of hypoglycaemia.

Results

F0632 is the only dose-response study showing that a low dose of mecasermin 60 mg b.i.d. was not sufficient in the treatment of primary IGFD. The mean annualised growth rate of these children prior to study enrolment was 1.2 cm/yr (range 0.45 to 2 cm/yr). The mean height SD score at baseline was -7.8 (range -10.7 to -5.8) and the mean standardised height -7.8 SD, ranging from -10.7 to -5.8 SD. Mean growth rate at 12 months was 5.4 ± 2.3 (SD) cm/yr (range 2.4 to 8.4 cm/yr) but standardised heights remained below normal (-7.9 ± 2.1, range –11.4 to –5.8).

The concern on the minimal effective dose of mecasermin due to insufficient data at the moment of evaluation has been addressed in the SPC section 4.2 and the collection of further data to establish the lowest effective dose is included in the post-authorisation follow up measures.

- Main studies

Study F0375g: A phase III, randomized, double-blind, placebo controlled, crossover, multicentre study of rhIGF-1 in children with short stature due to growth hormone insensitivity syndrome (GHIS)

Study F0206s: Study F0206s: Prolonged Treatment with rhIGF-1 in Children with Growth Hormone Insensitivity Syndrome (GHIS)

Study F0671g: A Phase 3, Open-label, Multi-center Study of rhIGF-1 in Children with Short Stature due to Growth Hormone Insensitivity Syndrome (GHIS)

Study 1419: A study of long-term recombinant human insulin-like growth factor-1 (rhIGF-1) treatment of children with short stature due to primary IGF-1 deficiency

METHODS

Study Participants

Subjects with growth failure due to severe Primary IGFD associated with either GH receptor defects or GH gene-deletion defects and anti GH antibodies were eligible for enrolment subjects in the US and in 21 other countries were enrolled.

The main primary criteria for enrolment in these studies were a) height standard deviation score < -2; b) evidence that the short stature would not be effectively treated by growth hormone (growth hormone sufficiency, non-responsiveness to growth hormone treatment, growth hormone gene deletion together with antibodies to growth hormone); c) pre-dose IGF-1 standard deviation score < -2 for subjects with growth hormone sufficiency and d) growth rate of < 50th percentile for age for ≥6 months prior to study entry.

Studies F0375g, F0671s and F0632g requested for GHIS, gene-deletion type only, the presence of GH antibodies to exogenous GH with a binding capacity greater than 10 μg/ml.

The exclusion criteria were similar for all studies:

- Active malignancy or any history of malignancy
- Growth failure due to other reasons such as disorder of genitourinary, cardiopulmonary, gastrointestinal, or nervous system; other endocrine disorders, including diabetes mellitus; nutritional/vitamin deficiencies, chondrodystrophies, or a known dysmorphic syndrome
- Treatment with any corticosteroids or other medications that influence growth
- Treatment with any other investigational drug within 30 days of this study
- ”Clinically significant”* Abnormal electrocardiogram (ECG) or a history of “clinically significant”* cardiac arrhythmia

* stated only in study 1419

Treatments

- **F0375g -** rhIGF-I initiated at 80 µg/kg and increased to 120 µg/kg if tolerated, given as SC injections BID. Injections were given immediately before breakfast (8 am) and dinner (6 pm). Open-label rhIGF-I was administered at a dose of 80 µg/kg SC BID on day 3 of the baseline visit. If tolerated, rhIGF-I 120 µg/kg SC BID was given on days 4 and 6. If the subject experienced symptoms of hypoglycaemia at either of these dose levels, the dose was decreased by 20µg/kg.
- **F0206s -** Starting dose 40 µg/kg SC BID, and increased over 2 days to 120 µg/kg SC BID. The dose for one subject was reduced to 80 µg/kg SC BID due to hypoglycaemia.
- **F0671g -** rhIGF-I doses of 80, 100, or 120 µg/kg SC BID on days 3, 4, and 5 respectively. Once the appropriate dose, based on acute tolerability (i.e. hypoglycaemia) was determined, the subject received this dose for 2 years unless no benefit (i.e. annualized growth rate of < 2.5 cm/yr over baseline based on measurements at 6-month intervals) was seen or an adverse event required discontinuation. If 80 µg/kg SC BID was not well tolerated a lower dose could be used after discussion between the investigator and the sponsor.
- **1419 -** Starting dose between 60 and 80 µg/kg SC BID, and if tolerated increased to 120 µg/kg BID.

Duration of treatment

- **F0375g -** Subjects received placebo or rhIGF-I for 6 months and after a 3-months washout crossed over to the alternative treatment. Upon completion of the 15-month blinded study, subjects received open-label rhIGF-I for 1 additional year.
- **F0206s -** 24 months
- **F0671g -** 24 months
- **1419 -** Mean duration of treatment was 3.9 ± 3.2 years and the median 3.0 years, representing a total of 274 subject-years of therapy (study is ongoing).

Objectives

- **F0375g** - to determine if replacement therapy with rhIGF-I given twice daily (BID) by SC injection to children with GHIS was safe and effective in improving linear growth
- **F0206s** - to evaluate the long-term safety and efficacy of rhIGF-I in children with short stature due to GHIS
- **F0671g** - to determine if replacement therapy with rhIGF-I administered twice daily (BID) by subcutaneous (SC) injection continued to be safe and effective in improving statural growth
- **1419** - to evaluate the efficacy and safety of long-term replacement therapy with mecasermin in children with primary IGF-I deficiency (IGFD)

Outcomes/endpoints

- **F0375g:** the primary efficacy measure was linear growth rate. The secondary efficacy measure was the change in standardized height**.**
  Safety: was assessed by report of adverse events (AEs), physical examination, review of clinical laboratory evaluations, antibodies to IGF-I, and reports of hypoglycaemia. Special safety assessments (i.e. GFR, echocardiogram, kidney and spleen ultrasounds) were also performed
- **F0206s:** the primary efficacy outcome measure was growth rate. Changes in height SDs, weight, pubertal stage, bone age, and bone mineral density as measured by DEXA were also examined.
  Safety: was assessed by report AEs, physical examination, and review of clinical laboratory evaluations. Additional evaluations included renal and spleen ultrasound, facial photographs, DEXA scan and echocardiography.
- **F0671g:** the primary measure of efficacy was annual growth rate over the first and second years of treatment.
  Safety: was assessed by report of AEs, physical examination, review of clinical laboratory evaluations, antibodies to IGF-I, and reports of hypoglycaemia. Additional evaluations included

spleen and renal ultrasounds, audiometry, echocardiograms, measures of kidney function and bone mineral density by DEXA.

- **1419: E**fficacy and efficacy-related variables include height velocity SD scores, height SD scores and bone ages.
  Safety: was evaluated on the basis of AEs and clinical laboratory tests, vital signs and relevant physical examinations. Special safety assessments (i.e. GFR, echocardiogram, kidney and spleen ultrasounds) were also performed in some subjects.

Sample size

76 subjects enrolled in one or more of these 5 studies.

Randomisation
Randomisation was only performed in F0375g, however the randomisation method is not clear as it was not presented.

Blinding (masking)

Only the crossover study F0375g was placebo-controlled and blinded. Only data of 4 trial subjects were analyzed.

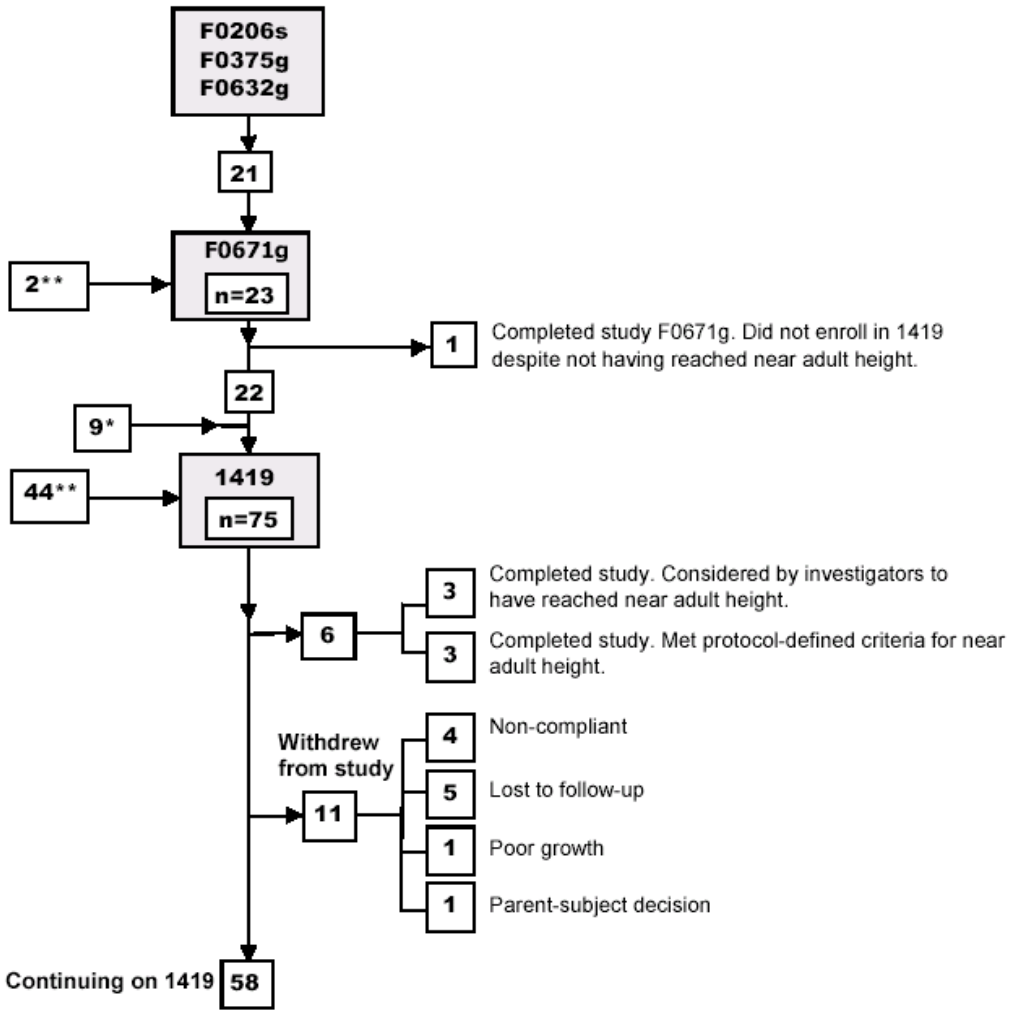
Statistical methods

Due to ethical concerns, there was no control group and the efficacy of mecasermin was assessed with respect to pre-treatment growth velocity. Data are expressed as the mean ± standard deviations, and means are compared using paired Student's t test, with $P < 0.05$ considered significant. The efficacy analysis was supplemented by height velocity SD scores in order to also compare height velocities with height velocities expected for age-matched children in the general population. A similar analysis was carried out for height SD score as a secondary endpoint.

RESULTS

Participant flow

Figure 2.7.3.2.5-1:Disposition of Subjects as of 07 April 2005



Source: **1419 Study Report Appendix 16.2.1**

Recruitment

- **F0375g**. 8 subjects were randomized of which 4 completed both of the 6-month double-blind treatment period and 6 to 12 months of the open-label phase. Three subjects (2 in the placebo group and 1 in the mecasermin group) completed only the first 6-month phase. Two of these subjects (1 placebo and 1 mecasermin treated) continued with open-label mecasermin treatment in the extension phase. The other subject (placebo group) transferred to study F0632g (after completing the 6-month placebo period).
- **F0206s**. 8 subjects were enrolled. All subjects completed the study.
- **F0671g**. 40 subjects were to be enrolled. 23 subjects (21 from prior studies and 2 naïve to treatment) were enrolled. The study was discontinued prematurely due to the discontinuation of the rhIGF-I development program at Genentech Inc. At the time of study termination, all 23 subjects had been enrolled and received rhIGF-I. 22 subjects had completed all study-specified visits. 1 subject did not return for a final visit when the study was discontinued prematurely. All available data were retrieved and data analysis is based on data from all 23 subjects.

- **1419**. 76 subjects enrolled in one or more of these 5 studies, only one of these dropped out prior to the initiation of **1419.** Many these subjects had been continuously treated with mecasermin for many years, and had transferred form one protocol to another when one protocol ended. In particular, all subjects enrolled in studies F0206s, F0375g, and F0632g were later enrolled in study F0671g. All subjects (except one) enrolled in F0671g, were later enrolled in study 1419.

Conduct of the studies

The study plans of the studies F0206s and F0375g were amended. The protocol of the latter study was changed 4 times affecting exclusion criteria, minimum age for entry, frequency of follow up visits, study extension, and decrease the daily dose.

Baseline data

The table below shows the Demographics and Baseline Characteristics (Numerical Variables) for Subjects with at least One Year of Treatment (n=62).

	Count	Mean	SD	Minimum	Maximum
Pretreatment age (Chronological, years)	62	6.8	3.8	1.7	15.2
Enrollment IGF-1 (ng/mL)	57	21.6	20.4	0.2	82.1
Enrollment IGF-1 SD score	57	-4.3	1.6	-9.5	-0.7
Pretreatment height (cm)	62	85.0	15.3	61.3	133.1
Pretreatment height SD score	62	-6.7	1.8	-12.1	-2.8
Pretreatment height velocity (cm/yr)	59	2.8	1.8	0.0	7.7
Pretreatment height velocity SD score	59	-3.3	1.7	-6.6	0.9
Enrollment weight (kg)	60	12.6	6.0	5.8	35.0
Enrollment BMI (kg/m2)	60	16.6	2.5	12.8	24.6
Enrollment BMI SD score	58	-0.1	1.2	-3.1	2.2
Pretreatment bone age (years)	50	3.9	2.8	0.1	12.3
Enrollment maximum IGF-1 from IGF-1 generation test (ng/mL)	36	21.9	24.8	0.5	115.0
Enrollment maximum IGF-1 SDS from IGF-1 generation test	36	-4.4	2.0	-8.9	-0.5
Enrollment maximum GH level: Laron-type phenotype subjects (ng/mL)	51	59.0	45.9	10.0	209.0

Pretreatment and enrollment dates are the same except for 4 subjects randomized to first receive placebo in study F0375g.
SD, standard deviation.

Numbers analysed

See Participant flow and Recruitment sections.

Outcomes and estimation

F0375g was the only randomised, double-blind, placebo-controlled and cross-over study, all other studies were single-arm uncontrolled studies. The mean growth rate for the 6 months prior to study entry was 3.4 cm/yr (range 1.0 - 5.6 cm/yr). The mean height SD score at baseline was -6.5 (-9.6 to -2.9). Only four out of a total of eight enrolled subjects completed this trial. One of these four subjects had similar growth rate both during placebo and rhIGF-1 treatment. Only results of active treatment period were included into the integrated study report.

In study F0206s Baseline height standard scores (SDS) were –3.4 to –7.0 (mean -5.6) referring to a severe growth failure. During the first year of therapy, mean height velocity increased 2.4-fold to 9.3cm/yr (mean height velocity SD score, +3.8). During the second year, mean height velocity declined to 6.2 cm/yr (mean ht. velocity SD score, +0.5). One subject treated for 3 years grew at

nearly the same rate as in the second year. The average change in height SD score after 2 (or 3) years of therapy was +1.2 (range, 2.1 to –0.3). Statural growth was accompanied by weight gain. The length of kidney length increased rapidly during therapy, but no structural anomalies or changes in renal function were observed.

In F0671g height increased by 10.8 cm ± 2.8 during 24 months. Twenty-one of 23 subjects had been treated with rhIGF-1 for 6 months to several years prior to enrollment. Growth increments in this study were consistent with that expected in a group of subjects previously treated with rhIGF-1.

In study 1419 **t**he 61 primary IGFD subjects treated for at least one year had marked short stature at baseline, with height SD scores ranging from -12.1 to -2.8 (mean -6.7). These patients had elevated basal or stimulated serum GH levels associated with markedly low serum IGF-1 SD scores (mean -4.3, range -9.5 to -0.7), confirming their diagnoses of Primary IGFD.

During the first year of therapy, the mean ± SD for height velocity was improved from 2.8 ± 1.8 cm/yr to 8.0 ± 2.2 cm/yr ($p < 0.0001$ by paired t-test) and the mean ± SD for height velocity SD score was improved from -3.3 ± 1.7 to +1.9 ± 3.0 ($p < 0.0001$ by t-test). First year mean ± SD for height SD score improved from -6.7 ± 1.8 to -5.9 ± 1.8 ($p < 0.0001$). Statistically significant improvements in mean height velocity ($p < 0.005$), mean height velocity SD score ($p < 0.0001$), and mean cumulative change in height SD score ($p < 0.0001$) were observed for at least 6 years, and in some cases after 8 years of therapy. Final height appeared to improve in subjects completing therapy. The growth response to mecasermin was similar for all subjects regardless of the severity of their disease (height SD score -12 to -3) prior to treatment (Figure 1).

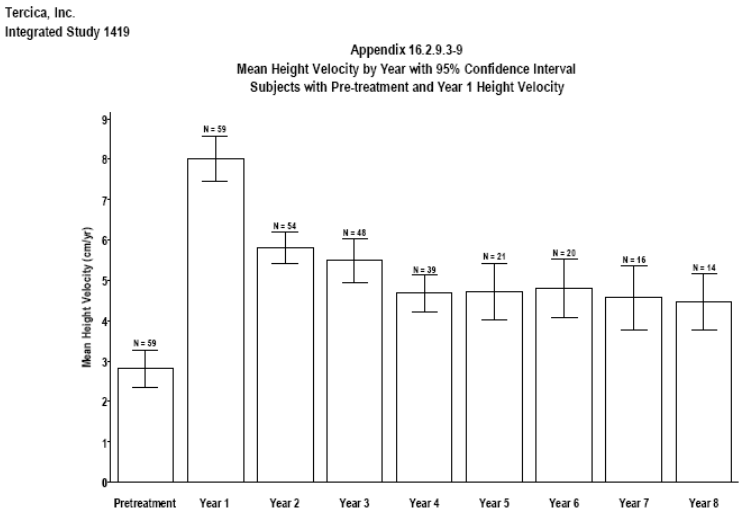


Figure 1. Mean height velocity for pretreatment year and post treatment years 1 to 8 using all data for each year.

Analyses of Height Velocity

- The mean difference in year one height velocity between males (n=38) and females (n=24((t-test p=0,41)
- Between subjects with GH gene deletion (n=7) * and subjects with Laron Syndrome phenotype (n = 53)
- Between age and year one height velocity in treatment – naïve subjects (n=62, p= 0,54) was not significant.

- Analysis performed across trials (pooled analyses and meta-analysis)

In the study report 1419 the results obtained from all clinical trials are reviewed and analyzed. The efficacy results from the pooled data can be seen in the table below:

Annual Height Results by Number of Years Treated with INCRELEX

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
N	58	58	48	38	23	21	20	16	13
Mean (SD)	2,8 (1,8)	8,0 (2,2)	5,8 (1,5)	5,5 (1,8)	4,7 (1,6)	4,7 (1,6)	4,8 (1,5)	4,6 (1,5)	4,3 (1,1)
Mean (SD) for change from pre-Tx		+5,2 (2,6)	+2,9 (2,4)	+2,3 (2,4)	+1,5 (2,2)	+1,5 (1,8)	+1,5 (1,7)	+1,0 (2,1)	+0,7 (2,5)
P-value for change from pre-Tx [1]		<0,0001	<0,0001	<0,0001	0,0045	0,0015	0,0009	0,0897	0,3059
Height Velocity SDS									
N	58	58	47	37	22	19	18	15	11
Mean (SD)	-3,3 (1,7)	1,9 (3,0)	-0,2 (1,6)	-0,2 (2,0)	-0,7 (2,1)	-0,6 (2,1)	-0,4 (1,4)	-0,4 (1,9)	-04 (1,9)
Mean (SD) for change from pre-Tx		+5,2 (3,1)	+3,1 (2,3)	+2,9 (2,3)	+2,2 (2,2)	+2,5 2,2)	(1,7)+2,7	+2,5 (2,1)	+2,7 (2,8)
Height SDS									
N	61	61	51	40	24	21	20	16	13
Mean (SD)	-6,7 (1,8)	-5,9 (1,8)	-5,6 (1,8)	-5,4 (1,8)	-5,5 (1,9)	-5,6 (1,8)	-5,4 (1,8)	-5,2 (2,0)	-5,2 (2,0)
Mean (SD) for change from pre-Tx		+0,8 (0,5)	+1,2 (0,8)	+1,4 (1,1)	+1,3 (1,2)	+1,4 (1,3)	+1,4 (1,2)	+1,4 (1,1)	+1,5 (1,1)

Pre-Tx= Pre-treatment; SD= Standard Deviation; SDS = Standard Deviation Score

[1] P-values for comparison versus pre-Tx values are computed using paired t-tests.

- Clinical studies in special populations

No studies have been conducted in children with renal impairment, nor to determine the effect of hepatic impairment on the pharmacokinetics of mecasermin.

- Discussion on clinical efficacy

The incidence and rate of inhibitor formation and its clinical significance, or more precisely, its impact on the efficacy of the product during long term IGF-1 treatment has not been clarified yet. The number of subjects available for analysis was small and the methods used for assessing anti IGF.-1 antibodies were not validated. According to the CHMP recommendation additional monitoring measures are required and presented in the Risk Management by the Applicant.

During the assessment there were concerns that the putative immunogenicity of the product was not sufficiently addressed in the application. Mecasermin antibodies were investigated in selected toxicology studies using ELISA methodology, but the bioanalytical methods/validation reports were not available for assessment. The test methods for detection of IGF-1 antibodies were not adequately described and validated. The Applicant provided the data requested on the antibody detection methods. However, it still remains unclear if the immunogenicity of the product proposed to be marketed is comparable to those of the materials manufactured previously. It is acknowledged that this issue cannot be totally solved. Therefore the immunogenicity of the product proposed to be marketed will be monitored. This is addressed in the Risk Management Plan.

Concerns were raised on the efficacy and safety results in study 1419 due to varying rhIGF-1 materials used in the patient population and the fact that the patients were collected from several studies. A total of 75 patients were included in the study, 44 of which were naïve to IGF-1 treatment. They received rhIGF-1 material of comparable quality. The remaining patients received rhIGF-1 material, for which equal quality and comparability was not initially demonstrated.

The Applicant performed some further analysis comparing the efficacy and safety results from the 44 patients who received exclusively ps material both to the overall group and also to the remaining 23

patients. The assessment showed that the efficacy results for the 44-subject cohort were similar to the results in the cohort of 23 subjects enrolled prior to study 1419. There were statistically significant increases in height velocity from baseline in each of the 4 years of follow-up in each cohort. The AE rates are generally lower in the 44-subject cohort. Therefore, this analysis does not suggest any specific safety issue with the ps (periplasmic secretion) material.

During the procedure the Applicant submitted efficacy documentation for the indication 'children with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH', which initially was insufficiently described in the dossier.

Height velocity information for years 1 to 8 was presented for the cohorts of severe Primary IGF-1 deficiency and growth hormone gene deletion subjects with a pre-treatment height velocity and a subsequent height velocity was submitted. Changes in height velocity from pre-treatment were statistically significant in both cohorts through 6 years and had positive differences from pre-treatment in years 7 and 8. Height velocities in the two cohorts were similar at all times. It was considered that even though the sample size was small the results did not show any discrepancy between the two groups

The results of the presented studies are in favour of the efficacy of the drug in the claimed indication, primary IGFD. However extensive discussion was needed in an effort to restrict the indication to this very rare and specific population.

Five aspects of the indication wording were reviewed during the procedure:
1. The name of the condition, i.e. growth hormone insensitivity syndrome, rather than severe primary IGF-1 deficiency,
2. The requirement to document specific genetic defects by molecular techniques,
3. The need of rhGH treatment trial prior to rhIGF-1 treatment,
4. The requirement for elevated GH, rather than normal or elevated GH,
5. The threshold of -3.0 for basal IGF-1 SDS.

The name of the condition as "Severe Primary IGFD" was considered acceptable with the condition that the diagnosis of the patients is based on very strict anthropometrical and biochemical criteria. The proposal for height standard deviation score -< -3,0; as a "cut-off" value was considered acceptable. The proposed basal IGF-1 SDS -<-3,0 as the diagnostic threshold after discussions based on the great variability of the normal value of the plasma IGF-1 level (age, gender etc.) and the fact that to establish its normal range should require a large number of samples was accepted as: "below the 2,5th percentile for age and gender". Further aspects such as the need for appropriate references necessary for IGF-1 assay standardisation, and the recommendation of an IGF-1 generation test to further strengthen the diagnosis of IGFD should be taken into account. The requirement to have rhGH treatment prior to starting rhIGF-1 therapy was considered to be unrealistic.

The need for documenting specific genetic defects by molecular techniques was discussed. The final conclusion was that even though genetic and molecular defect testing to strengthen the diagnosis would be of great use, the reality at this moment in time is that in many cases it may not feasible to routinely identify the genetic defect(s) causing short stature and therefore to allocate therapy based on genetic testing. Therefore this point was taken out of the indication.

To further ensure the correct usage according to the indication all secondary causes of IGF-1 deficiency (e.g. growth hormone deficiency or other causes such as malnutrition, hypothyroidism, or chronic disease) must be ruled out prior to initiation of treatment.

Comprehensive data on the efficacy of the medicinal product is lacking, particularly affecting the potential effect of immunogenicity on long-term growth. Due to the rarity of the disease this data cannot reasonably be expected to be provided. As such the product was considered by the CHMP to be approvable only under exceptional circumstances.

Clinical safety

- Patient exposure

A total of 1,516 subjects were enrolled in sponsored mecasermin clinical trials for indications including Primary IGFD, type 1 or type 2 diabetes mellitus, HIV cachexia, or as healthy individuals in pharmacokinetic studies.

Clinical studies were also conducted by other rhIGF-1 manufacturers. These include data reported in the literature from rhIGF-1 treatment of approximately 57 European, Ecuadorean, and Middle Eastern children with severe Primary IGFD.

The primary evaluation of mecasermin safety in subjects with severe Primary IGFD is gathered from the 5 studies that form the integrated 1419 Study Report. Safety information derived from other studies is not integrated with safety information from the paediatric statural studies in severe Primary IGFD. The rationale for this is that the populations in these supporting studies (late adolescent, adult, and elderly subjects) and the route of mecasermin administration (IV) in many of the studies are not representative of the indication that is the focus of this application. In addition, the adverse events experienced in the supporting studies are substantially influenced by the coexisting morbidities of these diseases, and the use of numerous concomitant medications.

Safety data from a total of 76 subjects with severe Primary IGFD, representing 321 patient-years of exposure to mecasermin and a mean duration of exposure of 4.4 yrs, are used to assess safety in this indication. The median duration of treatment is 4.0 years and the mean is 4.4 ± 3.1 years.

- Adverse events

Sixty subjects (79%) reported at least one adverse event (AE) during treatment. In the early studies, follow-up visits were more frequent. As experience was gained with the safety profile of mecasermin, visit intervals lengthened and AE reporting, particularly in the investigator-sponsored study, became more focused on those particular events that had been identified as possibly or probably associated with mecasermin therapy. The table below summarizes all AEs by MedDRA system organ class for safety evaluable subjects, defined as all enrolled subjects who received at least one dose of mecasermin.

The most common AEs included hypoglycaemia, lipohypertrophy at injection sites, tonsillar hypertrophy, headache and transient intracranial hypertension. This AE profile is similar to that seen in several other rhIGF-1 treated severe Primary IGFD cohorts.

Adverse Events by System Organ Class for All Subjects (n=76)

	Related	Total
Subjects reporting at least one adverse event	51 (67%)	60 (79%)
Metabolism and nutrition disorders	37 (49%)	40 (53%)
General disorders and administration site conditions	28 (37%)	32 (42%)
Infections and infestations	14 (18%)	32 (42%)
Respiratory, thoracic and mediastinal disorders	23 (30%)	32 (42%)
Nervous system disorders	18 (24%)	28 (37%)
Gastrointestinal disorders	8 (11%)	25 (33%)
Ear and labyrinth disorders	19 (25%)	23 (30%)
Investigations	15 (20%)	23 (30%)
Musculoskeletal and connective tissue disorders	10 (13%)	23 (30%)
Skin and subcutaneous tissue disorders	3 (4%)	19 (25%)
Blood and lymphatic system disorders	8 (11%)	16 (21%)
Eye disorders	4 (5%)	13 (17%)
Surgical and medical procedures	9 (12%)	12 (16%)
Injury, poisoning, and procedural complications	0 (0%)	11 (14%)
Reproductive system and breast disorders	3 (4%)	10 (13%)
Cardiac disorders	8 (11%)	9 (12%)
Congenital, familial, and genetic disorders	4 (5%)	9 (12%)
Psychiatric disorders	5 (7%)	8 (11%)
Renal and urinary disorders	2 (3%)	8 (11%)
Endocrine disorders	0 (0%)	2 (3%)
Hepatobiliary disorders	0 (0%)	1 (1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0%)	1 (1%)
Social circumstances	0 (0%)	1 (1%)
Vascular disorders	0 (0%)	1 (1%)

Hypoglycaemia

In study 1419 one or more episodes of hypoglycaemia were reported in 37 subjects (49%) during treatment with mecasermin. Of these 37 subjects, 12 (32%) had a history of hypoglycaemia prior to treatment. Six subjects experienced severe hypoglycaemia and hypoglycaemic seizure was reported in 3 subjects. In a placebo-controlled one-year study of patients with severe Primary IGFD, an equal incidence of hypoglycaemia was seen in rhIGF-1 and placebo-treated groups.

In mecasermin-treated subjects, hypoglycaemia occurred more commonly in younger, shorter subjects with a prior history of spontaneous hypoglycaemia. There was no difference in the severity of the underlying IGF-1 deficiency when subjects experiencing hypoglycaemia were compared to those who did not report hypoglycaemia. This AE was also more common in the first month of treatment then subsequently waned despite treatment continuing. The association of hypoglycaemia in younger children and those with inadequate caloric intake has been previously reported, and was usually dose dependent. In addition, in the sponsored studies described in this application, as well as studies reported in the literature, hypoglycaemia was avoided by ensuring the injection schedule for rhIGF-1 coincided with meals.

Tonsillar Hypertrophy and Associated Adverse Events

Snoring, generally beginning in the first year of treatment, was reported in 17 subjects (22%). Tonsillar hypertrophy resulting in upper airway congestion was reported in 13 subjects (17%) during the first 1-2 years of treatment with little further tonsillar growth in subsequent years. Tonsillectomy/adenoidectomy was performed in 8 subjects; 2 subjects had obstructive sleep apnea that

resolved after the procedure. Tonsillar and adenoidal hypertrophy has been reported during rhIGF-1 treatment of other severe Primary IGFD cohorts, presumably due to IGF-1 stimulating the immune system. In addition to the potential for snoring and upper airway obstruction, it is possible that the growth of oropharyngeal lymphoidal tissue led to a compromise of eustacian tube function and hearing acuity. Middle ear infusions were reported in 10 subjects (13%), otitis media in 14 subjects (18%); serous otitis media in 4 (5%) subjects, and ear infections in 4 subjects (5%).

Lipohypertrophy

Twenty-four subjects (32%) experienced lipohypertrophy at injection sites. This event was associated with lack of proper rotation of injection sites and resolved when injections were properly dispersed. Lipohypertrophy has been reported in other rhIGF-1 treatment cohorts.

Headache and intracranial hypertension (papilledema)

Headache was reported by 21 subjects (28%) during treatment with mecasermin. In a 6 month study of placebo vs. rhIGF-1 treatment in subjects with severe Primary IGFD, headaches were noted equally in both treatment groups. Headache with papilledema, nausea, and vomiting was observed in 3 mecasermin-treated subjects. Two of these subjects, twin siblings with GH gene deletion, had evidence on MRI of long standing hydrocephalus and had a presumptive diagnosis of intracranial hypertension. Their symptoms resolved without interruption of mecasermin treatment. In the third subject, symptoms resolved following lumbar puncture to reduce cerebral spinal fluid pressure and therapy was temporarily interrupted with resumption at a lower dose without recurrence of symptoms.

Changes in Organ Size and Function

Because of the animal data showing increased renal, spleen and cardiac size following mecasermin treatment these organs were evaluated by echocardiogram or ultrasound in study 1419. Among 36 subjects who had echocardiograms, there were no consistent findings suggestive of mecasermin-associated cardiac abnormalities and treatment was not discontinued or interrupted in any patient due to echocardiographic abnormalities. In all subjects, renal lengths increased substantially as the subjects grew and aged. When compared to normative data, the last available renal length SD scores exceeded the upper limit of normal (ie, were > 2) in only 2 subjects, 1 of whom one had a last renal size SD score for age of +2.6, and the other of whom had a last renal size SD score for age of +2.5. Overall, the mean renal size SD score for age at last evaluation was -1.8 ± 2.4**.** No structural abnormalities were observed on ultrasound and there was no evidence of renal dysfunction in any subject while on the study drug. Over a mean ± SD period of 4.3 ± 1.5 years between first and last renal ultrasound examinations, the mean ± SD for serum creatinine increased from 0.53 ± 0.1 mg/dL to 0.60 ± 0.14 mg/dL.

Spleen size was also evaluated and compared to the normal mean. Baseline splenic length was below the 10^{th} percentile for age in 20 of 23 subjects. Over 2 to 7 years of serial monitoring, spleen length did not appear to change notably from baseline to last visit in 8 subjects. Splenic length remained (or became) below the 10^{th} percentile in 16 subjects, became (or remained) normal in 5 subjects, and exceeded the 90^{th} percentile (by less than 1 cm) in 2 subjects.

Changes in Facial Appearance

Soft tissue swelling mimicking acromegaloid changes in facial appearance has been reported to be associated with mecasermin treatment of children with severe Primary IGFD. However, in 8 children followed by cephalometric measurements, mecasermin treatment for up to 6 years resulted in catch-up growth of facial bones, with no evidence of acromegaloid bony changes. In study 1419 analysis of mandibular cephalometric x-rays performed in a subset of subjects showed no evidence of acromegaloid growth of facial bones.

Neoplasia

There were no reports of neoplasia among patients treated with mecasermin in severe Primary IGFD studies. The single adverse event report coded to "neoplasia" in the MedDRA system represented a new wart.

Immunogenicity

Anti-IGF-1 antibodies were observed in 11 of 23 children with severe Primary IGFD tested during the first year of therapy. However, no clinical consequences of these antibodies were observed (e.g., allergic reactions or attenuation of growth).

- Serious adverse event/deaths/other significant events

Nine serious adverse events (SAE) were reported for 6 subjects in study 1419. Details are provided below.

Tonsillar hypertrophy: Patient was hospitalized for an adenotonsillectomy. The event was considered to be related to study drug by the investigator.

Severe pneumonia with empyema: Patient was hospitalized, treatment included oxygen and evacuation of the infection. Antibiotics were administered for 30 days with resolution of the infection. The pneumonia was considered unrelated to study drug by the investigator.

Tricuspid insufficiency: based on results of an echocardiogram. The investigator considered the event to be possibly related to study drug. This subject also had a generalized seizure reported as an adverse event. The seizure was reported to be unrelated to study drug by the investigator.

Febrile seizures associated with a tooth abscess; patient was hospitalized. This subject was also hospitalized for a skull fracture related to trauma. Both adverse events were reported as unrelated to study drug by the investigators.

Seizure-like activity accompanied by loss of consciousness, successfully treated with glucagon with no change in study drug administration. This subject had 3 additional episodes of hypoglycaemic seizures considered related to study drug. This patient had a history of hypoglycaemic seizures prior to mecasermin treatment and, on therapy, had seizures which were associated with inadequate food intake; these were not categorized as severe adverse events and were reported as unlikely to be related to study drug. This subject was also hospitalized for flank pain on another occasion where he was diagnosed with renal calculi and treated with herbal tea. The event was reported to be possibly related to study drug, which continued uninterrupted.

Appendicitis with appendectomy. The event was considered not related to study drug. Treatment with mecasermin was not interrupted.

There were no deaths reported in study 1419.

Three deaths (one subject with type 1 diabetes and 2 with type 2 diabetes) were reported in other studies or the immediate post-treatment follow-up. Details are provided below.

Type 1 diabetes mellitus
In study F0695g a 35-year old female with a 27-year history of type 1 DM and who was in the placebo group, died on Day 86. The cause of death was cardiopulmonary arrest secondary to advanced artherosclerotic heart disease. The death was considered related to diabetes and unrelated to study drug.

Type 2 diabetes mellitus
There was one death during the follow-up period of study F0625g. A 47 year old male suffered severe head injuries including a subdural haematoma and died in the hospital where he had been placed in a

drug-induced coma for neurological stabilization. The death was considered by the investigator to be unrelated mecasermin treatment.
A 67 year old female previously enrolled in study F0685g died 6 weeks after cessation of the study due to a myocardial infarction. The event was considered unrelated to prior mecasermin treatment.

- Laboratory findings

Routine serial laboratory evaluations were available for 23 subjects. Sporadic laboratory evaluations are available for an additional 16 subjects. At baseline, approximately 33% of subjects had low haematocrit and 36% had a low haemoglobin value. In most of the subjects, anaemia resolved during the course of treatment.

Serial total cholesterol and triglyceride levels were followed in 37 subjects. In general, levels of both analytes rose with age, although there was considerable fluctuation between the first and last values. Elevated serum cholesterol was the more frequent abnormality; the mean ± SD for first serum cholesterol level was 170.0 ± 36.5 mg/dL, and the last was 191.0 ± 30.5 mg/dL.

There were no consistent increases in liver function tests associated with mecasermin treatment although two subjects had abnormal AST prior to treatment and had increases in both ALT and AST to 3-5 times normal for age and sex on two consecutive visits. These values subsequently returned to near baseline without interruption of treatment.

- Safety in special populations

No gender specific AEs were found.

No formal analyses of the effect of ethnicity on IGF-1 safety were conducted. There were no obvious differences in safety related to dosing of mecasermin in ethnic groups.

In addition to the experience with mecasermin in severe Primary IGFD, more than 1500 subjects have been enrolled in studies of Genentech-manufactured mecasermin in a number of clinical indications such as type 1 and type 2 DM and HIV cachexia, or as healthy volunteers in PK studies. The largest groups of subjects were those paediatric and adult subjects with type 1 or type 2 DM. Some types of AEs such as peripheral oedema, jaw pain, back pain, arthralgia, nausea and dizziness were reported more frequently in the overall type 1 and type 2 DM cohorts treated with mecasermin (age up to 73 years) than in the subset of paediatric subjects (≤18 years of age). There was also a dose-dependent increase in the incidence of some of these events that occurred more frequently in subjects randomised to the highest doses. There were no deaths in any of the studies that were considered to be related to mecasermin treatment.

No studies have been conducted to determine the effects of mecasermin on an unborn child. Therefore, there is insufficient medical information to determine whether there are significant risks to a foetus. A negative pregnancy test and education about adequate contraception are recommended for all women of childbearing potential prior to treatment with mecasermin.

- Safety related to drug-drug interactions and other interactions

No in vitro or in vivo drug interaction studies were conducted for mecasermin.

- Discontinuation due to adverse events

No discontinuations due to adverse events were reported.

- Post marketing experience

No postmarketing data are available.

Other rhIGF-1 preparations have been registered and used in paediatric patients with growth hormone insensitivity. According to the Applicant, no unexpected safety issues have arisen in over 10 years of use.

In 1994, mecasermin (Pharmacia, now Pfizer) was approved for the treatment of growth hormone insensitivity in paediatric patients in Europe. In 1995, mecasermin (Somazon) received regulatory approval and was marketed by Fujisawa in Japan. Somazon was approved by regulatory authorities for the treatment of dwarfism in paediatric patients. The product is still marketed in Japan.

- Discussion on clinical safety

The most common adverse events included hypoglycaemia, lipohypertrophy at injection sites, tonsillar hypertrophy, headache and transient intracranial hypertension. This adverse event profile is similar to that seen in several other rhIGF-1 treated severe Primary IGFD cohorts.

The most important potentially limiting adverse event is hypoglycaemia. To address this safety concern it is recommended that children with severe Primary IGFD should receive a meal or a snack at the time of a mecasermin injection. In addition the patients and their care givers will be instructed how to treat hypoglycaemia. The SPC includes information about injection of glucagon as a treatment for hypoglycaemia. The RMP includes specific risk minimisation to this respect, including the development of educational material.

Children with severe forms of severe Primary IGFD frequently have mid-facial hypoplasia, with correspondingly small airways. Tonsillar hypertrophy was observed, presumably as a consequence of IGF-1 stimulation of the immune system. In addition, the growth of facial and oropharyngeal structures may not advance as rapidly as lymphoid tissue growth, leading to snoring and, in rare circumstances, sleep apnea. On the basis of these findings, monitoring of severe Primary IGFD patients for development of obstructive upper airways disease, including sleep apnea, is needed.
Mecasermin may also affect the growth of oropharyngeal lymphoidal tissue which leads to a compromise of eustacian tube function and hearing acuity.

Transient intracranial hypertension has been reported during treatment of severe Primary IGFD with rhIGF-1, and has resolved with either no change or a lowering of the rhIGF-1 dose. In study 1419, intracranial hypertension was reported. Pharmacovigilance and risk minimisation activities will be put in place to gain further information on this safety concern once the product is marketed.

Changes in organ size and function were observed during the clinical development. In F0206s the length of kidney increased rapidly during therapy. Less pronounced effects were seen when renal length is plotted against age-related standards. Ultrasound examination revealed no structural anomalies in kidneys. All patients experienced rapid growth of the spleen early in therapy, which decreased during the 2nd and 3rd year to a normal rate in six patients. In two patients, spleen growth reached the 90th percentile for age. Safety data from 1419 revealed cases of cardiac hypertrophy which were not clearly associated with the dose of mecasermin or with the age of the patient and were not easily predicted.

This data, though not supporting a disproportionate growth in organ size or the need to conduct long term structure function studies produced certain concern. It is agreed that regarding the renal and spleen growth the normal careful follow-up of these patients is sufficient. However follow-up of the cardiac growth by means of an echocardiogram in these patients has been included both in the SPC and the RMP.

The reported increased risk of cancer associated with blood levels of endogenous IGF-1 in the upper quartile of the normal range is less than 2- fold as shown by a recent meta-analysis. It is assumed that this increased risk is due to life long high blood IGF-1 levels. However, in the intended indication, blood IGF-1 levels are very low and it is the intent to bring these levels into the normal range and therefore to normalize blood IGF-1 levels. In addition, the length of treatment in the Tercica short stature study was for 4 years. Even if treatment were for 7 years, this may only represent 10% of the

lifespan. It can be assumed that for the other 90% of the lifespan IGF-1 blood levels would be subnormal. It is may therefore be assumed that the above risk will likely be less than in the general population, since exposure will not be life long, but only during childhood. In IGF-1 deficient patients, however, the object of replacement therapy with rhIGF-1 is to achieve normal blood IGF-1 levels, so one might predict that rhIGF-1 therapy should not increase their cancer risk above that of the normal population.

In 2002, data published from the two largest international surveillance databases of rhGH treatment, with a total of some 86,000 patients on rhGH, representing almost 250,000 treatment years, demonstrated the safety of rhGH treatment, even with long-term use, rhGH treatment has not been associated with an increased risk of cancer.

As a replacement growth factor though, INCRELEX is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued if evidence of neoplasia develops; additionally the follow up any neoplasia is considered in the risk management plan.

Comprehensive data on the safety of the medicinal product is lacking, particularly affecting the long term toxicity and possible occurrence of malignancies. Due to the rarity of the disease this data cannot reasonably be expected to be provided. As such the product was considered by the CHMP to be approvable only under exceptional circumstances.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Hypoglycaemia	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section 4.4 Warning INCRELEX should be administered before or after a meal. Pay special attention to young children, children with history of hypoglycaemia, and children with inconsistent food intake. Patients should avoid high risk activities within 2-3 hours after dosing particularly after initiation of treatment. At treatment initiation, the physician should educate the patient on the signs, symptoms, and treatment of hypoglycaemia including injection of glucagon. If a person with severe hypoglycaemia is unconscious or otherwise unable to ingest food normally, an injection of glucagon may be required. Medical attention should be sought for such episodes. Persons with a history of severe hypoglycaemia should have glucagon available. SPC Section Undesirable effects Hypoglycaemia is the most frequently

		reported adverse drug reaction. The thirty-six subjects (47%) who had one or more episodes of hypoglycaemia included 4 subjects who had hypoglycaemic seizure on one or more occasion. Of the 36 subjects, 12 (23%) had a history of hypoglycaemia prior to beginning treatment. The frequency of hypoglycaemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycaemia was generally avoided when a meal or snack was consumed either shortly before or after the administration of INCRELEX. Education material: Patient card for weight and dose. Dose calculator
Lipohypertrophy at Injection Sites	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section Undesirable effects Injection site hypertrophy occurred in 24 subjects (32%). This reaction was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the conditions resolved. Education material: Patient card for Lipohypertrophy
Tonsillar hypertrophy and Associated Adverse Events	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section 4.4 Warning Lymphoid tissue (e.g., tonsillar) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of INCRELEX. Patients should have examinations periodically and at the occurrence of clinical symptoms to rule out such potential complications or to initiate appropriate treatment. SPC Section 4.8 Undesirable effects Tonsillar hypertrophy was noted in 12 (16%) subjects, particularly in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years. Educational material: Patient card for Tonsillar hypertrophy and Associated Adverse Events
Headache and Intracranial Hypertension (Papilloedema)	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section 4.4 Warning Intracranial hypertension (IH) with papilloedema, visual changes, headache, nausea and/or vomiting has been reported in patients treated with INCRELEX, as has been reported with therapeutic GH administration. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination is recommended at the initiation, periodically during the course of INCRELEX therapy and at the occurrence of clinical symptoms. SPC Section 4.8 Undesirable effects Intracranial hypertension occurred in three subjects (4%). In two subjects the events resolved without interruption of INCRELEX

		treatment. INCRELEX treatment was discontinued in the third subject and resumed later at a lower dose without recurrence. Educational material: Patient card for Headache and Intracranial Hypertension (Papilloedema)
Changes in Organ Size and Function (including cardiomegaly)	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section 4.4 Echocardiogram is recommended before initiation of Increlex treatment in all patients. Patients who terminate treatment because of epiphyseal closure should also have an echocardiogram. Patients with abnormal echocardiogram findings or cardiovascular symptoms should be followed regularly with echocardiogram procedures. SPC Section 4.8, Undesirable effects, Table 1
Immunogenicity	Routine pharmacovigilance On suspicion of immunogenicity, patient samples sent to Tercica for anti-IGF-1 antibody analysis; Surveillance study Review of incidence, severity and duration every 6 months;	SPC Section 4.4 Warning Persons who have allergic reactions to injected IGF-1, who have unexpectedly high blood values of IGF-1 after injection, or who fail to show a growth response may be having an antibody response to injected IGF-1. In such instances, follow the instructions for antibody testing. SPC Section 4.8 Undesirable effects As with all protein pharmaceuticals, some patients may develop antibodies to INCRELEX. Anti-IGF-1 antibodies were observed in 11 of 23 children with severe Primary IGFD tested during the first year of therapy. However, no clinical consequences of these antibodies were observed (e.g., allergic reactions or attenuation of growth). Educational material: Immunogenicity sampling information will be provided to physicians
Allergic Reactions	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months	SPC Section 4.4 Warning As with any exogenous protein administration, local or systemic allergic reactions may occur. Parents and patients should be informed that such reactions are possible and that if an allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought. Educational material: Patient card for Allergic reactions
Scoliosis and Slipped Capital Femoral Epiphysis	Routine pharmacovigilance	SPC Section 4.4 Warning Slipped capital femoral epiphysis and progression of scoliosis can occur in patients who experience rapid growth. These conditions and other symptoms and signs known to be associated with GH treatment in general should be monitored during INCRELEX treatment. Any patient with the onset of a limp or complaint of hip or knee pain should be evaluated.

		Educational material: Patient card for Scoliosis
Neoplasia	Routine pharmacovigilance Surveillance study Review of incidence, severity and duration every 6 months; Surveillance sub-study for long-term safety; neoplasia follow-up, biennial	SPC Section 5.3 Preclinical safety data, Carcinogenesis Education material: Patient card for neoplasia
Medication Error	Routine pharmacovigilance	Education material: Patient card for weight and dose. Dose calculator

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: See as detailed in section 2.3

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

During the evaluation of INCRELEX, major objections were identified. These concerned:
-The putative immunogenic potential of mecasermin based on insufficient structural characterisation of the protein and due to lacking information concerning impurity levels of commercial and clinical lots.
-The comparability between the commercial rhIGHF-1 batches and the early developmental batches.
-The stability of the drug substance and the drug product.

Satisfactory justification has been provided to resolve these objections. Other minor concerns have been adequately addressed, however several commitments are made by the Applicant, and several follow up measures are defined to provide further information post approval. In conclusion, all quality issues are resolved.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

The principal findings following the SC administration of mecasermin in the nonclinical pharmacodynamic studies were increases in bone growth in GH and IGF-1 deficient animal models, acute decreases in blood glucose, increases in body weight, and enhancement of immune function. These finding are considered relevant to human therapeutic use.

Mecasermin antibodies were investigated in selected toxicology studies using ELISA methodology, but the bioanalytical methods/validation reports were not available for evaluation. Due to this omission, the capability of the antibody assay method to detect anti-IGF-1 antibodies could not be fully assessed.

The applicant has adequately investigated toxicity of mecasermin, showing that in general, the safety margin in clinical situations is not high. The major observations in toxicological studies were increases in body weight and organ weights and hypoglycaemia. Mecasermin was not found be genotoxic. The mecasermin carcinogenicity study demonstrated that lifetime administration of mecasermin was associated with an increased incidence of benign neoplasms of the skin and adrenal gland (pheochromocytomas) and mammary fibroadenomas and carcinomas. The extrapolation of the results from this study to humans is uncertain.

Efficacy

The minimal effective dose of mecasermin has not been sufficiently established due to insufficient data at the moment of evaluation. Collection of further data to establish this dose is included in the post-authorisation follow up measures.

The results of the main pivotal studies are in favour of the efficacy of the drug in the claimed indication, primary IGFD. The incidence and rate of inhibitor formation and its clinical significance, or more precisely, its impact on the efficacy of the product during long term IGF-1 treatment has not been clarified yet. The number of subjects available for analysis was small and the methods used for assessing anti IGF.-1 antibodies were not validated. According to the CHMP recommendation additional monitoring measures are required and presented in the Risk Management by the Applicant. Potential immunogenicity will be further investigated in the post-authorisation phase.

Height velocities between severe Primary IGF-1 deficiency subjects and growth hormone gene deletion subjects were compared and seen to be similar at all times. This showed that even though the numbers were small, efficacy in the indication 'children with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH' was sufficiently demonstrated.

Safety

The most common adverse events in the clinical studies have been hypoglycaemia, lipohypertrophy at injection sites, tonsillar hypertrophy, headache and transient intracranial hypertension. Additionally, concern was raised on the kidney, spleen and cardiac growth. These adverse events will continue to be monitored in the post-authorisation phase.

The issue of the putative immunogenicity of the product proposed to be marketed cannot be completely addressed at this stage. The long-term safety has to be confirmed in the post-authorisation setting.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

User consultation was not performed. It has been included as part of the follow-up measures to be conducted by the Applicant.

Risk-benefit assessment

In conclusion, the risk-benefit assessment seems to be favourable based on the current knowledge, but it needs to be reassessed yearly as more data will be gathered. The CHMP considers that a marketing authorisation only under exceptional circumstances should be recommended since the indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the efficacy and safety of the medicinal product at this stage.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and that additional risk minimisation activities were required: see as detailed in section 2.3

Recommendation

During the post-opinion phase the Applicant notified the withdrawal of the indication referring to patients with "growth hormone (GH) gene deletion that have developed neutralizing antibodies to GH" as it did not fall within the scope of the orphan indication.

Based on the CHMP review of data on quality, safety and efficacy, and the above mentioned withdrawal, the CHMP considered by consensus that the risk-benefit balance of INCRELEX in the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD); severe Primary IGFD being defined by:

- height standard deviation score ≤ –3.0 and
- basal IGF-1 levels below the 2.5th percentile for age and gender and
- GH sufficiency
- Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids

was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.