



European Medicines Agency  
*Pre-authorisation Evaluation of Medicines for Human Use*

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**WITHDRAWAL ASSESSMENT REPORT  
FOR**

**Iplex  
(mecasermin rinfabate)**

**EMEA/H/C/754**

Day 120 Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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## LIST OF ABBREVIATIONS

AE	ADVERSE EVENT
ALS	ACID LABILE SUBUNIT
AUC	AREA UNDER THE CURVE
AUC <sub>(0-24)</sub>	AREA UNDER THE CURVE OF SERUM CONCENTRATION VS. TIME DATA FROM TIME = 0 TO 24 HOURS
BID	TWICE DAILY
BMI	BODY MASS INDEX
CDP#1	COMMERCIAL DRUG PRODUCT PRODUCED AT AVECIA, LTD., BILLINGHAM, UK
CDP#2	COMMERCIAL DRUG PRODUCT PRODUCED AT INSMED THERAPEUTIC PROTEINS, BOULDER, CO
CI	CONFIDENCE INTERVAL
CL/F	APPARENT TOTAL CLEARANCE
C <sub>MAX</sub>	MAXIMUM OBSERVED SERUM CONCENTRATION
C <sub>MIN</sub>	MINIMUM OBSERVED SERUM CONCENTRATION
COMP	COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS
CRF	CASE RECORD FORM
DDP	DEVELOPMENT DRUG PRODUCT PRODUCED AT INSMED, SANTA CLARA, CA
ELISA	ENZYME LINKED IMMUNOSORBENT ASSAY
FDA	FOOD AND DRUG ADMINISTRATION
GH	GROWTH HORMONE
GHBP	GROWTH HORMONE BINDING PROTEIN
GHD-IA	GH DEFICIENCY TYPE IA
GHI	GROWTH HORMONE INSENSITIVITY
GHIS	GROWTH HORMONE INSENSITIVITY SYNDROME
GHRD	GROWTH HORMONE RECEPTOR DEFICIENCY
HV	HEIGHT VELOCITY
IGFBP-3	INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3
IGF-I	INSULIN-LIKE GROWTH FACTOR-I
IGF-II	INSULIN-LIKE GROWTH FACTOR-II
IGF-IR	INSULIN-LIKE GROWTH FACTOR-I RECEPTOR
IR	INSULIN RECEPTOR

KD	KILODALTON
KEL	ELIMINATION RATE CONSTANT
NM	NANOMOLAR
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (UK)
PK	PHARMACOKINETIC(S)
QD	ONCE DAILY
QHS	EVERY BEDTIME
RHGH	RECOMBINANT HUMAN GROWTH HORMONE
RHIGFBP-3	RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3
RHIGF-I	RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-I
RHIGF-I/RHIGFBP-3	RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-I/RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 COMPLEX
RMP	RISK MANAGEMENT PLAN
SAE	SERIOUS ADVERSE EVENT
S.C.	SUBCUTANEOUS
SD	STANDARD DEVIATION
SDS	STANDARD DEVIATION SCORE
SOP	STANDARD OPERATING PROCEDURE
T <sub>1/2</sub>	HALF-LIFE
T <sub>MAX</sub>	TIME OF OBSERVED MAXIMUM SERUM CONCENTRATION
V <sub>D/F</sub>	APPARENT VOLUME OF DISTRIBUTION

## I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP consider that the application for Iplex, an orphan medicinal product, in the treatment of primary growth hormone insensitivity (PGHI) and growth hormone (GH) gene deletion with neutralising antibodies to GH, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies.

### *Quality aspects*

- Process validation at Insmed Boulder is incomplete.
- Genetic stability of cell banks has not been demonstrated.
- The presence of contamination of the MCB/WCB should be justified.
- The components of discrete batches cannot be identified.
- Process parameters are still to be defined.
- The binding affinity of IGF-1 to IGFBP-3 is unknown.
- The levels of impurities in the product were found to be too high.
- There is insufficient data to demonstrate that the drug products produced at the different sites are comparable.
- The stability data provided do not justify the proposed use of the product.

### *Non clinical aspects*

- The significance of the drug accumulation reported during the long term repeated dose toxicity studies has not been addressed.
- There is concern over the carcinogenic potential of the product, which has not been adequately addressed.

### *Clinical aspects*

- The evidence that the patient population of the pivotal trial is representative of the targeted indication is missing.
- The optimal dose regimen has not been established.
- The persistence of the treatment effect has not been established beyond 12 months.
- There is evidence suggesting that the two drug products providing efficacy and safety data are not comparable whereas no data are available with the commercial product.
- The analysis of organ growth data from ultrasound examination has not been provided.

A product specific GMP inspection is requested before license approval.

## II. EXECUTIVE SUMMARY

### II.1 Problem statement

Conditions that are characterized by complete or partial insensitivity to growth hormone (GH), i.e. where GH is unable to exert its biological effects, can be defined by clinical and biochemical features of IGF-I deficiency associated with normal or elevated GH secretion. Primary GH insensitivity syndrome (PGHIS), also called Laron syndrome, includes hereditary/congenital defects that can be due to GH receptor deficiency, abnormalities of GH signal transduction or primary defects of synthesis of IGF-I. Secondary GHI syndromes are acquired, sometimes transitory conditions, that can be due to circulating

antibodies to GH that inhibit GH action (GH gene deletion patients treated with GH), antibodies to the GH receptor, and conditions such as malnutrition, liver disease, uncontrolled diabetes mellitus, and sepsis.

PGHIS is an extremely rare disease with an estimated prevalence worldwide of approximately 200-350 patients. The classical form of Laron syndrome, which is inherited as an autosomal recessive trait, has extreme short stature (final heights of 120-130 cm) with the characteristic facial phenotype of mid-facial hypoplasia, frontal bossing, and depressed nasal bridge. However, a worldwide search for patients with GHI has identified less severe cases (atypical forms) indicative of a previously unexpected degree of heterogeneity. The development of clear criteria for the diagnosis of GHIS has therefore been crucial in defining patients with this syndrome, who could benefit from treatment with rhIGF-I, and a scoring system has been established (Savage 1993, Blum 1994). It is based upon the following criteria, each one having a score of 1 and a total score of 5 points or more indicating GHIS.

- Height SDS  $\leq$  -3
- Basal GH  $>$  4 or 10 mU/L
- Basal IGFs  
IGF-I  $<$  0.1 percentile ( $\sim$  -3 SDS) or  $<$  50  $\mu$ g/L  
IGFBP-3  $<$  -2 or -3 SDS
- IGF-I generation  
IGF-I increase  $<$  15  $\mu$ g/L  
IGFBP-3 increase  $<$  0.4 mg/L
- GH binding  $<$  10%

Because IGF-I is the primary mediator of the growth promoting actions of GH, replacement therapy with rhIGF-I bypasses the blockade of GH action and improves statural growth. However, due to shared structural homology between IGF-I and insulin and their respective receptors IGF-I can activate both the IGF-I receptor as well as the insulin receptor and has the potential to induce acute insulin-like side effects such as hypoglycaemia. Also the short circulating half life of free IGF-I has led to the general practice of administering rhIGF-I in two daily injections to achieve useful systemic exposure and to minimize side effects.

The rationale for developing the complex of rhIGF-I/rhIGFBP-3 is stated to be based on the normal physiology of the IGF system. In healthy individuals, endogenous IGF-I is  $>$ 98% bound to binding proteins that form a ternary complex with another binding protein called acid labile subunit (ALS). This ternary complex creates a circulating reservoir that significantly extends the half life of IGF-I and controls its interaction with the IGF-I receptor and insulin receptor. The principal binding protein required to form the ternary complex is IGFBP-3. Therefore, Iplex was developed to replace both IGF-I and IGFBP-3 in a complex to closely mimic the normal physiology of the IGF system. The administration of this complex should theoretically have several advantages over that of free rhIGF-I. It should readily bind to ALS to form the ternary complex and while circulating as part of this complex rhIGF-I should have a decreased serum clearance. Moreover, it should be able to circulate at a very high concentration without inducing hypoglycaemia.

## II.2 About the product

Mecasermin rinfabate is a binary complex of human IGF-I and IGFBP-3, both produced by recombinant DNA technology in two separate *E. coli* strains. IGF-I consists of 70 amino acids in a single chain and IGFBP-3 consists of 264 amino acid residues; their amino acid sequence is identical to that of the endogenous proteins. IGFBP-3 from human plasma is glycosylated whereas rhIGFBP-3 produced in *E. coli* is non-glycosylated; however, they both bind IGF-I with similar affinities.

The target indications sought by the Applicant are primary GHI and GH gene deletion with neutralising antibodies to GH. These are exclusively paediatric indications.

The primary pharmacologic effect of IGF-I in children is the promotion of linear growth and the primary effect of IGFBP-3 in mecasermin rinfabate is the modulation of IGF-I action. Besides this effect, IGF-I possesses a broad range of biological activities, including anabolic effects, enhanced wound healing, promotion of bone formation, stimulation of lymphopoiesis, improved glucose tolerance and insulin sensitivity, motor neuron survival and sprouting, increased creatinine clearance, and recovery of renal function following ischemic injury. Therefore, a whole range of clinical studies have been conducted with mecasermin rinfabate, either sponsored by the company or by investigators, in such indications as post-surgical hip fracture, severe acute burns, type 1 & 2 diabetes mellitus, severe insulin resistance, HIV-associated Adipose Redistribution Syndrome, and Small for Gestational Age children.

Iplex is presented as a sterile 60 mg/mL solution (pH 5.5) supplied in single dose glass vials containing 36 mg of active in 0.6 mL of solution. The product is temperature sensitive and must be stored frozen at -70°C while in the distribution chain. Patients/parents are instructed to keep the medication frozen while transferring it to their home (e.g. on dry ice), where it has to be kept in their freezer for not more than 3 months. The product has to be thawed and used within 2 hours after the vial has reached room temperature.

The posology recommendations include a starting dose of 0.5 mg/kg once daily followed by a dose titration up to a maximum of 2 mg/kg daily based on measurement of IGF-I levels obtained 8-18 hours after dosing. An ELISA kit for this assay is commercially available.

### **II.3 The development programme**

This is a full application for a new active substance in line with the Commission Directive 2001/83 EC as amended. The centralised procedure (according to Regulation EC/726/2004) is mandatory (article 3 annex (1) biotech medicinal product). The Applicant requested an accelerated review of the submitted documentation of mecasermin rinfabate, which was not granted by the CHMP.

The application is complete. The main data are “original” data; however, because no comparative clinical trials were performed, the results obtained were compared to historical data published in the literature (“bibliographical references”).

A complication of this application is the historical multiple sites of manufacture. The drug substance was first produced at Inmed Santa Clara, Ca. USA, and was then moved to Avecia, Billingham, UK and was then transferred to Inmed, Boulder Co. USA (also called Inmed Therapeutic Proteins - ITP). The manufacturing process has evolved through many changes; the largest differences are between the drug substance produced by Inmed Santa Clara and that produced by Avecia and Inmed Boulder. The drug substance is produced and tested at the Inmed site at Boulder.

The phase I in healthy volunteers started in 1996 in the USA. The first single dose pharmacokinetic trial in GHIS was conducted in the UK in 2002-2003; the pivotal phase II/III trial was then started in June 2003 and is still ongoing. Due to the rarity of the disease, this trial is being conducted in a great number of centres (currently 18) from 11 countries. However, according to the last update, about half of the study population (15/36) has been recruited by two centres in Turkey. As previously mentioned, much larger studies have been conducted in a broad range of other indications, mostly in the USA; they have been used to support the safety of the product.

No scientific advice has been given at the European level. Regulatory Guidance and Advice was sought from the FDA and National European Union Agencies (France, The Netherlands, Sweden and the United Kingdom) regarding the pharmacokinetic and clinical studies and the wording of the indication.

Iplex was approved by the FDA in December 2005 with the following indications:

- severe primary IGF-I deficiency as defined by height standard deviation score (SDS)  $\leq$  -3 and

- basal IGF-I SDS  $\leq$  -3 and normal or elevated growth hormone; this includes patients with mutations in the GH receptor (GHR), post-signalling pathway, and IGF-I gene defects
- GH gene deletion with neutralising antibodies to GH.

## **II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles**

A product specific **GMP** inspection is requested before license approval. The GMP status of the Avecia site should be included by the Applicant as the current master and working cell banks were created there. The GMP status of the closed site Insmed Santa Clara was not included.

Toxicity studies with rhIGF-I/IGFBP-3 were conducted in compliance with **GLP**, with the exception of determinations of serum antibodies: these assays were performed by the Applicant in accordance with laboratory SOPs and study protocols. In addition, a number of studies with rhIGF-I are included in the dossier, which are termed 'Supportive Data' by the Applicant. Most studies are GLP compliant. However, two studies with rhIGF-I are included which describe investigations into its effects on xenografted tumour cell in nude mice and so may be considered mechanistic pharmacology studies, not subject to GLP requirements. In conclusion, GLP aspects are satisfactory.

According to the Applicant, all clinical studies have been conducted “according to the principles in the Declaration of Helsinki and the Guidelines for **GCP**.”

As already mentioned a single multicentre pivotal trial has been initiated in 18 centres; with the exception of the two Turkish centres they have only enrolled 1-2 patients each. A Steering Committee was established in order to review the screening data prior to enrolment of subjects, to grant exception waivers for subjects who did not meet all inclusion/exclusion criteria, to perform an ongoing review of accumulating safety and efficacy data, and to determine dosing adjustments throughout the trial. This committee is not independent since it consists of the Company’s Chief Scientific Officer, the Company’s Medical Director, and the three Coordinating Investigators.

Another issue is that, 17 months after the end of the first year of treatment, 8 subjects out of 17 were still waiting for country or local regulatory approval to resume treatment during the second year in the extension-study.

Overall, although the difficulties of conducting such a trial are acknowledged, some possible deficiencies have been identified, which have not been openly discussed by the Applicant in the text of the reports; these were in general of mediocre quality regarding both their presentation and their content.

## **II.5 General comments on the submitted dossier**

There is a general consensus amongst all assessors that the overall quality of the dossier is poor. In particular, a lot of interim or incomplete data have been submitted when more up-to-date information should be available; precise references to appendices and attachments are lacking; a lot of clinical statements are groundless and no critical comments can be found in the Overview; finally the Risk Management Plan is unacceptable and requires a complete rewrite.

# **III. SCIENTIFIC OVERVIEW AND DISCUSSION**

## **III.1 Quality aspects**

### **Drug substance**

The drug substance is manufactured at Iplex Therapeutic Proteins, Boulder Colorado, USA. A product specific inspection of this site has been requested. Clinical material presented in the dossier was also

manufactured at Avecia, Billingham, UK and the current master and working cell banks were created at Avecia and so the GMP status of this site has also been requested.

The Drug Substance described in the Quality Module is a complex of recombinant human Insulin-like Growth Factor-I and recombinant human Insulin-like Growth Factor Binding Protein-3 (rhIGF-I/rhIGFBP-3). The binary complex of IGF-I/IGFBP-3 further combines with a third circulating protein, once injected, the GH-dependent acid-labile subunit (ALS), to form a ternary complex of ~140-150 kD which represents the natural physiologic reservoir of IGF-I.

The components (intermediates) are manufactured separately by fermentation in *E. coli*.

The rhIGF-I is expressed as a fusion protein.

Validation data for the process performed at the intended manufacturing site is absent and this is unacceptable. Validation of the process at other sites was presented, but as the process changed with each move of site this validation data does not support the current manufacturing process.

Data concerning the stability of the vector is not presented in the dossier, only the intention to complete this work in the future. The data concerning the stability of the vector is a Ph Eur requirement and should be provided. This is a major deficiency.

It is reported that the master and working cell banks are infected. It is not known if this infection is an adventitious infection or is in some way required for the expression of the drug substance, an explanation has been requested.

The Applicant has defined some parts of the process as critical and others as key. A number of processes, which appear critical, have not been defined as such and the Applicant has been asked to justify why these processes are not critical. This is an important distinction as deviations from operating parameters for critical processes would lead to batch rejection whereas the same deficiency for a process described as key would only lead to an investigation, after which the batch could be released.

A complication of this application is the historical multiple sites of manufacture. The drug substance was first produced at Insmed Santa Clara Ca. USA and was then moved to Avecia, and was then transferred to Insmed, Boulder. The Applicant has attempted to demonstrate that the drug substance produced at each site is comparable. One difficulty is that there is very limited material from the Santa Clara and no opportunity to manufacture any more as this site has closed.

The Applicant has attempted to show comparability using analytical techniques such as mass spectrometry, differential scanning calorimetry (DSC) and peptide mapping. Analytical data indicated that material from the Santa Clara and Avecia sites was similar. Physical methods and bioassay data does not support a claim of comparability. In addition, tentative similarity has only been demonstrated on a limited number of batches and in the case of material produced at Insmed Santa Clara this evidence takes the form of one reference batch produced at this site. The greatest changes in manufacturing processes are between the Insmed Santa Clara site and the Avecia and Insmed Boulder sites and it is between these sites that the data regarding batch numbers is at its weakest. The comparability study presented does not conform to ICH Q5E and therefore does not demonstrate comparability.

The binding affinity of the recombinant products has not been compared with native proteins. The data concerning the rhIGF-I – rhIGFBP-3 binding affinity is based on a published report. It is not known whether the materials involved in this study were prepared by any of the three technologies described in the application. The published binding affinity data concerning IGF-1 and IGFBP-3 was not obtained using the Applicant's IGF-1 or IGFBP-3 and this study should be performed and the results compared to the binding affinities of native IGF-1 and IGFBP-3.

The drug substance specification appears justified although the bioassay limits are too wide and the biological activity when expressed as a ratio appears different for the intended manufacturing site

compared to previous manufacturing sites. The validation exercise of the assay for biological activity is incomplete and should be completed. The criterion of specificity should be revised.

The Applicant should introduce an assay that can detect the range of contaminants that are likely to be present and lower the levels of contaminants.

The stability data for drug substance appears adequate, if a justification for reducing the level of testing is justified, but the Applicant needs to confirm that distinct batches were used in this study and not just sub-batches of the same batch.

### **Drug product**

For manufacture of commercial Drug Product, bulk Drug Substance containers are withdrawn from  $\leq -70^{\circ}\text{C}$  storage, thawed for 36 hours at  $2-8^{\circ}\text{C}$  and filtered to yield bulk Drug Product, which is then filled. The drug product is then stored at  $\leq -70^{\circ}\text{C}$ .

The Applicant has demonstrated that the product is stable at  $-70^{\circ}\text{C}$  for 24 months. They have further claimed stability at  $-20^{\circ}\text{C}$  for 15 months, but have only presented data from 1 batch at 12 months where a number of data were out of specification during this period.

The product is also stable at  $2-8^{\circ}\text{C}$  for 3 months. There is 1 batch providing data for  $25^{\circ}\text{C}$ . The Applicant needs to justify why the stability studies do not mimic the cold chain progress of the product i.e.  $-70^{\circ}\text{C}$  to  $(-15^{\circ}\text{C} -1^{\circ}\text{C})$  to room temperature. The stability data does not justify the proposed use of the product, as it will progress to higher temperatures during its cold chain progression. An acceptable temperature range for the proposed storage of the product in the home freezers should be defined.

## **III.2 Non clinical aspects**

### **Pharmacology**

The primary pharmacodynamic effect of rhIGF-I/rhIGFBP-3 in the promotion of linear growth has been demonstrated in *in vivo* studies using the hypophysectomised, osteoporotic or calorically restricted rat as models. This has been supported by *in vitro* data with rhIGF-I.

The major secondary pharmacodynamic effect of rhIGF-I/rhIGFBP-3 is the serum glucose-lowering effect due to the structural and functional homology of IGF-I with insulin. Increased circulating levels of free IGF-I induce insulin-like effects by activating the insulin receptor in addition to the IGF-I receptor. A consequence is hypoglycaemia. The administration of rhIGF-I/rhIGFBP-3 complex reduced the acute hypoglycaemic effects of rhIGF-I in rats and monkeys. The Applicant did not refer to the pharmacological activity of rhIGF-I and its affinity for IGF-I receptors in these species. The source of material used in pharmacology studies was difficult to identify. The Applicant should address this.

No dedicated safety pharmacology studies have been conducted with rhIGF-I/rhIGFBP-3, although the cardiovascular and respiratory effects of rhIGF-I have been studied in the anaesthetised cat and conscious dog. The effects of rhIGF-I were slight under the test conditions employed and were similar to those observed with insulin. The Applicant should present an argument using kinetic data to justify the absence of a specific study with rhIGF-I/rhIGFBP-3. Additionally, adequate clinical data may obviate the need for further non-clinical testing with rhIGF-I/rhIGFBP-3.

The one drug-interaction study conducted revealed that rhIGF-I did not ameliorate doxorubicin-induced cardiotoxicity.

## Pharmacokinetics

Validation data for the kits used in preclinical kinetic studies are not provided. The pharmacokinetic parameters of IGF and IGFBP-3 following administration of rhIGF-I/rhIGFBP-3 have been investigated in the rat, monkey and pig by both the i.v. and s.c. routes. In all cases, the rate and extent of absorption for IGF-I increased in a dose-dependent manner. Following s.c. administration of rhIGF-I/rhIGFBP-3, serum IGF-I levels remained increased for several hours, whereas i.v. administration resulted in a relatively rapid decline. In general, the pharmacokinetic characterisation could be enhanced by further discussion by the Applicant of issues relating to the binding stability of the complex, glycosylation and the interaction with ALS.

The i.v. administration of equimolar doses of rhIGF-I, rhIGFBP-3 or rhIGF-I/rhIGFBP-3 in rats and monkeys revealed that systemic exposure to rhIGF-I is much greater following administration of rhIGF-I/rhIGFBP-3 compared to that for approximately equimolar doses of free rhIGF-I. The clearance of both IGF-I and IGFBP-3 was much slower following administration of rhIGF-I/rhIGFBP-3 than after administration of either protein alone. These findings may be attributed to the ability of the rhIGF-I/rhIGFBP-3 complex to bind to ALS in the circulation.

Two studies to compare the pharmacokinetics following administration of a batch manufactured by either the Inmed Santa Clara or the Avecia process conducted in rats revealed no significant pharmacokinetic differences in the parameters measured. In both studies the route of administration was s.c. and both studies were single dose studies.

No distribution studies were conducted with rhIGF-I/rhIGFBP-3. However a study conducted with rhIGF-I in mice revealed that following i.v. administration there was widespread distribution of radioactivity throughout the body, particularly in well vascularised tissues.

No metabolism studies have been conducted with rhIGF-I/rhIGFBP-3 or rhIGF-I. The anticipated effect is degradation to small peptides and amino acids.

One excretion study conducted with rhIGF-I/rhIGFBP-3 in monkeys revealed increased immunoreactive IGF-I in the urine at 72 hours after administration.

## Toxicology

The Applicant has performed a number of single and repeated dose toxicity studies with rhIGF-I and rhIGF-I/rhIGFBP-3. The studies were conducted in normal animals. There were no studies in relevant animal models such the hypophysectomised rat.

The single dose studies conducted with rhIGF-I/rhIGFBP-3 revealed that in the rat and monkey using the i.v. route of administration the main treatment related finding was hypoglycaemia. Single dose toxicity studies with rhIGF-I in the mouse and rat (i.v. route) or monkey (s.c. route) revealed no toxic effects at up to 80 and to 1 mg/kg respectively.

The repeated dose toxicity of rhIGF-I/rhIGFBP-3 has been studied in rats and monkeys for up to 90 days. Antibodies were detected in some rats from the control group: this finding should be explained by the Applicant. In rats, daily s.c. administration at doses up to 30 mg/kg resulted in dose dependent increases in body weight and an increase in the weight of lymphoid tissues, particularly the spleen, thymus and lymph nodes. It is regrettable that this study did not contain a toxicokinetic element. Similar effects were obtained following 90 consecutive days of administration to monkeys at dose levels up to 10 mg/kg/day. In monkeys there was an increase in lean body mass in all treated females and an increase in whole body bone mineral density in high dose males at the end of the treatment period. Accumulation was evident in repeated dose toxicity studies and has not been adequately explained by the Applicant.

Repeated dose toxicity studies with free rhIGF-I have been conducted for up to 3 weeks in mice and up to 26 weeks in rats and monkeys. In general the results of these studies were similar to those observed in the studies conducted with rhIGF-I/rhIGFBP-3 although in the case of rhIGF-I there were deaths which were attributed to hypoglycaemia; these were reported in both rat and monkey studies following both i.v. and s.c. routes of administration. All animals treated with rhIGF-I developed antibody titres throughout the treatment periods but these did not neutralise the mitogenic effect of the test compound. Whereas for the proposed indication, studies of 6 months' duration might be expected, the Applicant has provided insufficient justification for the adequacy of the 13 week studies that were reported. The possibility of additional long term general toxicity studies should be considered.

The anabolic effects following repeated dosing with rhIGF-I/rhIGFBP-3 and rhIGF-I were qualitatively similar and considered to result from the pharmacological effect of the test compounds. However, severe hypoglycaemia was noted on several occasions following dosing with rhIGF-I which resulted in some deaths, particularly in mice and rats at 10 mg/kg/day. These effects were not apparent in rats treated with rhIGF-I/rhIGFBP-3 at dose up to 30 mg/kg/day, although this dose is equivalent to only approximately 6 mg/kg/day rhIGF-I. With one exception, hypoglycaemic shock was noted in all monkeys treated at 1 mg/kg/day rhIGF-I when food was withheld. These effects were not observed in monkeys treated at 10 mg/kg/day rhIGF-I/rhIGFBP-3, a dose approximately equivalent to 2 mg/kg/day rhIGF-I.

No studies to assess the genotoxicity, carcinogenicity or reproductive and developmental toxicity of rhIGF-I/rhIGFBP-3 have been conducted. However, supporting data on genotoxicity, carcinogenicity and reproductive toxicity generated with free rhIGF-I have been submitted.

rhIGF-I was not genotoxic under the test conditions used. Such studies are not appropriate for protein products.

The results of a 2-year carcinogenicity study indicate that treatment with rhIGF-I at doses  $\geq$  4mg/kg/day in female rats and 10 mg/kg/day in male rats caused an increased frequency of several types of neoplasms. In view of the paucity of the data available it is not possible to evaluate the significance of these findings. Consequently, it is considered that the Applicant has not provided an appropriate assessment of carcinogenic potential of rhIGF-I/rhIGFBP-3. To determine whether there is merit in conducting standard rodent lifetime bioassays with rhIGF-I/rhIGFBP3, the Applicant is requested to present data from *in vitro* and/or *in vivo* tumour inhibition studies and, depending on the results of these studies, it can be determined whether carcinogenicity studies in rodents are warranted or not.

In the reproductive toxicity studies, rhIGF-I produced no adverse effects in the rat. By contrast, administration of rhIGF-I at the dose of 1.25 mg/kg/day to rabbits on days 6-18 of gestation produced a number of treatment related effects including an increased incidence of abortion, an increase in post-implantation loss, a reduction in the number of viable foetuses and an increase in foetal skeletal abnormalities. However, this compound is indicated for the paediatric population. The impact of the presence of the binding protein on these effects of rhIGF-I could be significant. Consequently, the Applicant should address this point further. Studies with rhIGF-I/rhIGFBP-3 are warranted.

A local tolerance study of rhIGF-I/rhIGFBP-3 in rats revealed mild to marked active inflammatory reaction involving the s.c. tissues, which was reversible following discontinuation of dosing. Considering this finding, results of a repeat assessment using the clinical product at the maximal clinical dose should be reported.

In Section 5.3 of the SPC the first sentence should be deleted until the concerns stated in Section VI below are adequately addressed. The statement that s.c. administration of rhIGF-I early during organogenesis resulted in an increased incidence of fetal loss but no fetal abnormalities in rabbits is a variance with the data. It may be deleted depending on results of additional work requested.

### III.3 Clinical aspects

#### Pharmacokinetics

##### Bioanalytical methods

Serum concentrations of IGF-I, IGFBP-3, IGF-II and ALS were all determined by ELISA assays using commercial kits. Free-IGF-I levels (i.e. not protein-bound) were measured using a specific commercial kit for free IGF-I. Some aspects of the validation of these methods by the Applicant or the kits' manufacturer are missing.

Antibodies to the complex rhIGF-I/rhIGFBP-3 and its components were measured by enzymatically amplified direct immunoassays

Six clinical studies provided pharmacokinetic data for mecasermin rinfabate. Four were conducted in healthy volunteers, including one in 12 elderly female using continuous subcutaneous infusion for 7 days, which is not especially relevant for the proposed indication and mode of administration. The three other studies were two intravenous dose escalation studies (one single and one multiple dose) performed in 12 and 17 subjects, respectively, and one bioequivalence study comparing one single subcutaneous dose of two commercial drug products manufactured at two different sites (CDP#1 and #2), the latter being the product to be marketed. Two studies were conducted in 9 children and adolescents with GHIS using various single subcutaneous doses with one comparison to supplied rhIGF-I and one comparison between drug development (DDP) and commercial drug (CDP#1) products.

The two phase I studies in healthy volunteers investigating the intravenous route (single and multiple dose) showed results consistent with saturable pharmacokinetics over a dose range of 0.3 to 6 mg/kg.

- An increase in systemic exposure to IGF-I and IGFBP-3 was observed, as reflected by increased C<sub>max</sub> and AUCs, but it was not dose-proportional.
- The apparent volume of distribution and total clearance of IGF-I increased with dose.
- The terminal half-lives of IGF-I (around 10-15 hours) and IGFBP-3 (around 3-5 hours) did not appear to be dose dependant. This difference in half-lives contradicts the assumption that IGF-I and IGFBP-3 are strongly associated *in vivo*.

The continuous subcutaneous infusion of 2 mg/kg/day for 7 days administered to elderly women resulted in unstable levels of IGF-I and IGFBP-3, which decreased after 3 days and became similar to those achieved with 1 mg/kg/day whereas dose proportionality was observed between 0.5 and 1 mg/kg/day.

Due to endogenous levels of IGF-I and IGFBP-3 as well as normal levels of ALS pharmacokinetic parameters estimated in healthy volunteers are likely to be erroneous and cannot replace studies in patients. Unfortunately, data in patients with GHIS are limited regarding both the number of patients involved (9) and the frequency of blood sampling. Inter-individual variations appeared substantial and at least partly related to the level of ALS. No formal dose-response study was performed and these limited data can only be considered as exploratory.

In children and adolescents with GHIS, single subcutaneous doses of 0.5, 1 and 2 mg/kg (containing 105 to 420 µg/kg of rhIGF-I) resulted in similar serum levels of IGF-I, which were generally comparable to those achieved at steady-state with 160 µg/kg of rhIGF-I injected alone in two daily doses. Patients with measurable serum ALS levels had higher C<sub>max</sub> and lower clearance values for IGF-I than patients without detectable ALS.

The pharmacokinetic profile presented in the SPC is derived from the only study where a biphasic absorption profile was observed. The pharmacokinetic parameters are estimated in 4 patients without any detectable level of ALS following the s.c. injection of 1 mg/kg of CDP#1. C<sub>max</sub> ranges from 107 to 153 ng/mL (mean = 133) and T<sub>max</sub> from 6 to 18 hours (mean = 11). The apparent volume of distribution is

around 1000 mL/kg. The half-life and total clearance of IGF-I range from 10 to 16 hours (mean = 13) and 50 to 56 mL/hr/kg (mean = 53), respectively.

Since the core data supporting efficacy and safety were generated with the drug development product the Applicant attempted to show that it was comparable to a first commercial drug product CDP#1 (in 4 patients), which was later compared to the final commercial drug product CDP#2 in a proper bioequivalence trial in 28 healthy volunteers. However, both trials failed to provide unequivocal pharmacokinetic evidence that the drug development product was bioequivalent to the commercial drug product to be marketed. There are no pharmacokinetic data available in patients with this latter product.

In all these studies the total amount of IGF-I in serum was measured and not the free (unbound) fraction, which is biologically active. The free IGF-I concentration profile was only determined in the healthy volunteers of the bioequivalence trial for the final commercial drug product CDP#2; most subjects had slightly supraphysiological levels of free IGF-I in contrast with the high levels reported in the literature following the administration of rhIGF-I alone.

#### Pharmacokinetic aspects not studied

The absolute bioavailability of the subcutaneous route for mecasermin rinfabate has not been determined. The bioavailability of rhIGF-I after subcutaneous administration in healthy volunteers has been reported to be close to 100%.

No specific study on drug metabolism has been conducted. It may be assumed that the metabolic fate of mecasermin rinfabate involves classical protein catabolism in both the liver and kidneys.

No interaction studies have been performed. However, based on its metabolism, the complex is an unlikely candidate for cytochrome mediated drug-drug interactions.

No data are available in patients with impaired renal or liver function. However, mecasermin rinfabate is expected to be metabolised through peptide hydrolysis and renal elimination is probably a minor pathway for clearance. Consequently, impaired liver or renal functions are not expected to affect the pharmacokinetics of the complex in a clinically significant way.

Steady-state pharmacokinetics and drug levels on chronic treatment have been studied in the clinical trial.

In conclusion, the main pharmacokinetic issues are:

- The limited amount and moderate quality of data in patients (none being obtained with the commercial product);
- The questionable bioequivalence of the commercial product and the drug development product, which provided the 12-month efficacy and safety data used as the basis for this application;
- The absence of data on free IGF-I in patients;
- The absence of a rationale for selecting the 1 mg/kg/day dose to start the clinical development in GHIS with a further increase to 2 mg/kg/day.

The influence of ALS on the pharmacokinetics of the product should be introduced in the SPC.

#### **Pharmacodynamics**

Since there is no known validated biomarker predictive of linear growth rate primary pharmacodynamic data are expected to be absent.

However, secondary pharmacodynamic data on carbohydrate metabolism could have been more extensive; the effect on insulin has not been studied. The effect of a single intravenous injection of mecasermin rinfabate on blood glucose was assessed in healthy volunteers. Four doses were tested: 0.3, 1,

3, and 6 mg/kg in four sequential cohorts. Blood glucose levels were stable after doses of 0.3 to 3 mg/kg. In the highest dose group one subject experienced a near syncope with pelvic cramps and hypoglycaemia; decrease in serum phosphorus was also observed. It was concluded that the maximum tolerated intravenous dose was 3 mg/kg.

In addition, bone turnover was assessed in elderly female treated for 7 days with continuous subcutaneous infusion of mecasermin rinfabate. The initial protocol planned to test three doses in sequential cohorts: 2, 4 and 6 mg/kg/day. Due to adverse reactions in the first group treated with 2 mg/kg/day (decreased serum phosphorus, daily intermittent headaches, nausea, and generalised body aches) the subsequent dose levels were decreased (0.5 and 1 mg/kg/day). Varying increases in markers of bone turnover were recorded, including serum bone-specific alkaline phosphatase, serum osteocalcin, serum procollagen peptide, urine N-telopeptides, and urine deoxypyridinolines. Concentration-time curves at the three different doses showed some increases above the placebo group, indicating an increase in bone resorption and formation but the fluctuations were considerable.

### **Clinical efficacy**

The Applicant has performed a single prospective open-labelled multicentre trial in three consecutive cohorts of patients treated with three different drug products. This is a 12-month trial followed by a 12-month extension, which is still ongoing.

- A drug development product (DDP) was administered for at least the first 12 months of the study to Cohort #1, which produced 12-month efficacy data (16 patients out of 19).
- An intended commercial product (CDP#1) was administered at the initiation of treatment to Cohort #2, which produced 6-month efficacy data (9 patients out of 10).
- The final commercial product (CDP#2) was administered to Cohort #3, which produced only 1-month safety data (7 patients).

The only major difference was that a fixed dose of 1 mg/kg/day was used in the first cohort whereas an amendment was later implemented that allowed for titration of dose up to 2 mg/kg/day based on serum IGF-I levels and safety profile.

### Patient population

Twenty-seven (27) pre-pubertal patients enrolled in the first two cohorts on the basis of low height, low IGF-I and IGFBP-3 levels, and high stimulated GH levels were reported as carriers of GHR defects (i.e. classical Laron syndrome); two patients were reported as GH gene deletion with neutralising antibodies. Overall, they were 17 boys and 12 girls, aged 3 to 15 years; the second cohort was more severely affected than the first one. Four patients were excluded from the primary efficacy analysis at 6 months because 1) three subjects had received less than 159 days of study drug [adverse drug reaction (2), lost to follow-up (1)], and 2) one subject withdrew consent after temporary treatment discontinuation due to possible adverse drug reaction.

### Method

Classical clinical growth parameters were measured with the primary endpoint being the change in height velocity (HV) compared to pre-treatment height velocity, which was estimated over the year preceding study entry. HV was calculated at each post-baseline visit (after 1, 3, 6, 9, 12 months) and annualised for that year of treatment. Secondary endpoints were change in height SDS, bone age SDS, sitting height, weight, head circumference, body mass index (BMI), predicted adult height standard deviation scores, and pubertal stage. Serum IGF-I, IGFBP-3, IGF-II and ALS concentrations were regularly checked. Although such an uncontrolled trial, is likely to overestimate the treatment effect this approach was considered acceptable in view of the known natural history of Laron syndrome and the difficulty of conducting a controlled trial in such a rare disease.

### Dose

In Cohort #1, the dose administered was 1 mg/kg/day except when it was decreased to 0.5 mg/kg/day in 5/19 patients due to adverse drug reaction or high IGF-I levels. Out of the 17 patients remaining in the study at the end of the first year, only 9 are still on treatment in the extension study because regulatory approval has not been obtained for the other 8 patients.

In Cohort #2, 9/10 patients had their dose increased from 1 to 2 mg/kg/day within the first 5 months.

### Results

*In Cohort #1 (16 patients)*, the mean increase in HV was estimated at 3.0 cm/yr with a 95% CI interval of [2.3, 3.7] over the first 12 months of treatment (mean pre-treatment HV = 3.4 cm/yr). However, it was obvious that the increase in HV was sharp in the very beginning of the treatment (1-3 months) but that this level of increase was not maintained during the following months. The mean height gain of 0.5 SDS at 12 months was statistically significant. A significant increase in bone age was also shown, which was higher than 1 year. All subjects remained pre-pubertal during treatment. IGF-I and IGFBP-3 levels gradually increased up to 9 and 6 months, respectively, and started to decline afterwards. In contrast, ALS levels rapidly declined in patients with baseline detectable levels, which may be indicative of the suppression of endogenous GH secretion by negative feedback of circulating rhIGF-I. IGF-I levels reached a high-normal range (>0 SD) in 11/19 patients during the second half of the treatment year.

*In Cohort #2 (9 patients)*, the mean increase in annualised HV was estimated at 6.6 cm/yr with a 95% CI interval of [4.6, 8.6] over the first 6 months of treatment (mean pre-treatment HV = 2.2 cm/yr); it had only been 4.0 cm/year in Cohort #1 over the same time period. In addition, the mean height gain was 0.4 SDS at 6 months. All subjects remained pre-pubertal during treatment. According to the Applicant these results are sufficient to support the dose titration scheme allowing to increase the dose up to 2 mg/kg/day based on IGF-I serum levels. The difference between the two cohorts is of borderline statistical significance ( $p = 0.033$ ) in the analysis performed by the Statistical Assessor. However, the cohorts were not randomised, they were different at baseline, the drug products were different, and more importantly, the height velocity was already higher in Cohort #2 during the initial months of treatment when all patients were still on 1 mg/kg/day. Furthermore, increases in IGF-I levels were quite similar in spite of the differences in doses.

### Steady-state pharmacokinetics of IGF-I

In both cohorts, some subjects underwent 24-hour blood surveillance at baseline, Month 3, and Month 6. In Cohort #2, 5 subjects were on 2 mg/kg/day and 2 on 1.5 mg/kg/day at Month 3; out of 6 subjects, they were all but one on 2 mg/kg/day at Month 6. Although inter-individual variations were broad these data showed progressive increase in serum IGF-I levels from baseline to Month 6.  $C_{min}$ ,  $C_{max}$ , AUC (0-24) increased whereas the apparent total clearance tended to decrease. Median values for the concentrations and AUC were comparable in both cohorts in spite of the difference in doses; median  $C_{max}$  and AUC increased by a factor of 3 to 7 over the first six months of treatment. These results indicate that steady-state serum levels are absolutely not predictable from single dose studies and pharmacokinetics in patients are governed by unknown factors.

### Antibody surveillance

Antibodies recognizing either the rhIGF-I/rhIGFBP-3 complex or its individual components were detected. Almost all patients from both cohorts (27/29) developed antibodies against the complex rhIGF-I/rhIGFBP-3; their titres appeared positively correlated with serum IGF-I and IGFBP-3 levels, which may provide a possible explanation for the sustained increase in drug levels (reduced clearance). Antibodies tested for their capacity to inhibit IGF-I bioactivity *in vitro* were not found to be neutralising (in 3 patients) and no correlation was observed between antibody titres and changes in HV. It is noteworthy that subjects treated in Cohort #2 with CDP #1 had substantially lower antibody titres than subjects in Cohort #1 with DDP.

A number of critical issues have been identified regarding the data submitted.

1. The study population was not clearly defined although the Applicant states that it is representative of the “indicated target population”.
  - The diagnosis of GHR deficiency (classical Laron syndrome) was not documented.
  - More liberal GHI criteria were used than those commonly applied in the GHI score; in particular, the IGF-I generation test was not required.
  - Other potential factors of poor growth (e. g. nutritional factors) were not excluded and seem to have been present in some cases.
  - There was no criterion regarding growth during the preceding year.
2. The optimal dose has not been established.
  - No data exist on 0.5 mg/kg/day.
  - The same IGF-I levels have been obtained with 1 and 2 mg/kg/day (up to 6 months) although with different drug products.
  - As a result, the objective of the dose titration has not been achieved since its rationale and guidelines were based on IGF-I levels.
  - There is no clinical evidence that the dose of 2 mg/kg/day is superior to 1 mg/kg/day; indeed, with these guidelines, most if not all patients end up with the highest dose.
3. A sustained effect has not been demonstrated.
  - 6 and 12-month data are not sufficient to evaluate a new growth promoting therapy.
  - This is especially critical in the present case where a very rapid spurt has been observed in the first 1-3 months followed by a rapid waning.
  - This is also important since the levels of IGF-I & IGFBP-3 started to decline in the second half of the first treatment year.
4. There is evidence of differences between the two drug products (DDP and CDP#1).
  - They show a different immunogenicity profile.
  - The same drug levels are achieved in spite of different doses, which may be related to the differences in immunogenicity.
  - This obviously raises the question about the (currently) unknown characteristics of the final commercial product (CDP#2).
5. The advantage of the complex over rhIGF-I alone is questionable.
  - Although no head to head comparison was performed, which would be difficult due to the rarity of the disease, historic comparison with published, or other data provided, shows that the 12-month results achieved in the first cohort (receiving 210 µg/kg/day of rhIGF-I) are in the low range of efficacy as compared to 80-240 µg/kg/day of rhIGF-I (in two injections).
  - At a dose of 2 mg/kg/day, which contains 420 µg/kg/day of IGF-I, the relative efficacy of the complex becomes highly questionable

It is also noted that the GH deletion indication is only supported by 2 patients.

In conclusion, there is a need for further data to support the claimed indication and dose recommendations:

- 24-month data in Cohort #1 and 12-month data in Cohort #2 (as supportive data)
- 12-month data with the commercial product (Cohort #3) (as pivotal data)
- convincing evidence of a difference between the two doses (1 vs 2 mg/kg/day) with the commercial product based on both clinical efficacy and drug levels
- 24-month data with the commercial product (post-approval commitment)

In addition, there is a need for more data regarding the long-term development of antibodies and their neutralising capacity.

## Clinical safety

The safety database encompasses 11 company-sponsored studies, with 305 subjects having received the active drug and 65 having received a placebo. The age range is broad, from 0 to 89 years; 81 children and adolescents have been exposed to the active drug and 19 to a placebo. The doses range from < 0.5 mg/kg to 6 mg/kg by intravenous route but only up to 2 mg/kg by subcutaneous route. However, most of these treatments were of short duration (less than 1 month) and only the pivotal trial in GHIS provides safety data for exposure longer than 3 months.

In addition, the Applicant has provided a summary of the information collected from an ongoing Named Patient Program (11 patients) and five investigator-sponsored clinical studies.

In the whole database, the most common adverse events (> 5% of all treated subjects) that were more frequent on active drug than on placebo were injection site reactions, headache, and back pain. Metabolic disturbances (hypoglycaemia, hypocalcaemia, hypokalaemia) occurred in a similar proportion of patients on active drug and placebo.

Four subjects died in the clinical trials (one in the GHIS trial) and one in the Named Patient Program; none of these deaths were considered related to study drug.

Serious adverse drug reactions were mainly reported in the GHIS trial: hypoglycaemia (2, including one episode in a patient with a history of postnatal hypoglycaemia with seizures who had not eaten after the injection); adeno-tonsillar hypertrophy (2), papilloedema (1) in a child with a ventriculo-peritoneal shunt, hepatomegaly (1). In addition, an increase in serum alkaline phosphatase and gamma-glutamyltransferase was reported in an elderly female (hip fracture trial) and an allergic reaction was reported in the HIV-associated Adipose Redistribution Syndrome investigator-sponsored study.

The last safety update for the GHIS trial included 36 patients: Cohort #1 (19 patients) with an exposure of up to 22.5 months, Cohort #2 (10 patients) with an average exposure of 8 months, and Cohort #3 (7 patients) with an exposure of approximately 1 month.

- Injection site reactions were by far the most frequent adverse drug reactions (almost all patients) and included a high prevalence of chronic cutaneous/subcutaneous changes (lipohypertrophy, hair growth, and hyper- or hypo-pigmentation).
- Hypoglycaemic episodes were reported in 11/36 (31%) patients but were generally rated as mild and asymptomatic. Four hypoglycaemic episodes were characterised as symptomatic including two cases that required acute intervention. They usually occurred in the morning (injection in the evening) and in the beginning of the treatment, i.e. at the dose of 1 mg/kg/day.
- Headache was reported in about 1 out of 5 patients; it is the most common adverse reaction to rhIGF-I, which may be related to a certain degree of water retention and transient increase in intracranial pressure.
- Adenoidal/tonsillar hypertrophy was reported in the same proportion of patients; in one case, tonsils were so enlarged at the occasion of a viral infection that the patient had to be intubated. Other events of organomegaly were observed, which might be more frequent with the highest dose (splenomegaly, hepatomegaly, goitre, multiple ovarian cysts).
- Finally, papilloedema was reported in 2 cases; this is a known reaction to GH and rhIGF-I.

Repeated ultrasound examination of the liver, spleen, and kidney showed evidence of catch-up growth but the Applicant has not provided a detailed and adequate analysis of these data.

Laboratory tests showed few abnormalities apart from transient increase in transaminases in 2 patients. Serum TSH levels tended to decrease during treatment.

It is noteworthy that the development of antibodies was not associated with any signs of allergic reactions.

In conclusion, most of the known adverse reactions to rhIGF-I have been observed with mecasermin rinfabate in spite of the limited size of the GHIS population with chronic exposition; the only notable exceptions (up to now) are facial nerve paresis and hypokalaemia. It is acknowledged that hypoglycaemia seems less severe but injection site reactions are much more frequent.

A number of safety issues have been identified. The most important is the limited information on chronic exposure, especially at the highest dose (2 mg/kg/day). Furthermore, there is no information on possible long-term toxicity; this is especially relevant in view of the effect of IGF-I on cell proliferation and the occurrence of neoplasms in animal carcinogenicity studies with rhIGF-I. In addition, facial soft tissue changes and mandibular growth have been described in the literature in association with long-term rhIGF-I treatment. The Applicant has no plan for long-term safety data collection in their Risk Management Plan.

Other issues include the lack of adequate analysis or studies regarding the effect of the treatment on:

- organ growth;
- GH secretion;
- body composition and fat mass.

#### **IV. ORPHAN MEDICINAL PRODUCTS**

On 20 June 2006 Iplex (mecasermin rinfabate or rhIGF-I/rhIGFBP-3) received two orphan designations in relation to the current application. The orphan indications are labelled as follows:

- Treatment of primary insulin-like growth factor-1 (IGF-I) deficiency due to molecular or genetic defects
- Treatment of patients with growth hormone (GH) gene deletion who have developed neutralising antibodies to GH

The first condition has an estimated prevalence of *less than 2 in 10,000 persons* in the Community; the second condition is even rarer with an estimated prevalence of *less than 0.01 in 10,000*. The ground for these designations was the absence of current satisfactory treatment authorised in the Community for patients affected by the condition.

#### **V. BENEFIT RISK ASSESSMENT**

The approval of mecasermin rinfabate is sought for two indications: primary growth hormone insensitivity (PGHI) and growth hormone (GH) gene deletion with neutralising antibodies to GH.

The Applicant has not estimated the target population but PGHI syndrome (PGHIS) is extremely rare (about 200-350 patients worldwide), which justifies the very limited size of the clinical trial conducted to support this application.

If the indication is clearly restricted to PGHIS as diagnosed on the basis of the GHI score, replacement therapy with rhIGF-I is fully justified because the extreme short stature of these patients is a major handicap and they do not respond to GH therapy. Based on more than 10 years of experience, rhIGF-I therapy results not only in improvement of height velocity, but also of bone formation, body composition, anabolism, physical performance, and psycho-social well-being.

Patients in the pivotal clinical trial were allegedly diagnosed with classical Laron syndrome due to a GH receptor defect, but the documentation of this diagnosis has not been provided. Regarding the other

indication, only two patients were recruited with this diagnosis but in this case also without documentation.

In spite of this diagnostic uncertainty the short-term efficacy results of mecasermin rinfabate appeared substantial in most patients with a very rapid spurt in height velocity during the first 3 months. This effect was not sustained afterwards although the benefit was still significant at the end of the first year of treatment (first cohort). Data from the second cohort are too limited in time (6 months) to allow any conclusion about a potentially more stable effect in this group. Therefore, there is a need for longer treatment duration (at least 2 years) to allow for reasonable confidence in the persistence of therapeutic benefit. In addition, since three different drug products have been used in the clinical trial and their comparability is questionable, there is a need for clinical data generated with the product to be marketed.

Furthermore, the Applicant recommends a dose-titration scheme based on target serum levels of IGF-I, which results in all patients receiving the highest dose of 2 mg/kg/day (second cohort). However, IGF-I levels achieved at the highest dose are quite similar to those achieved with 1 mg/kg/day. Therefore, the current data cannot support these dose recommendations. Moreover, efficacy results obtained at the dose of 2 mg/kg/day, which provides 420 µg/kg/day of rhIGF-I, are in the same range as those obtained with 80-240 µg/kg/day of rhIGF-I alone. Thus, the whole rationale of the complex appears questionable regarding the efficacy advantage.

Short-term safety data suggest that hypoglycaemia is less severe (if not less frequent) with the complex than with rhIGF-I alone. However, long-term safety data, which are still very limited (especially with the highest dose of 2 mg/kg/day), seem to indicate a similar safety profile; injection site reactions appear even more frequent. Finally, almost all patients develop antibodies to the complex, which contains 80% of binding protein for 20% of IGF-I; they do not seem to be deleterious in the short-term but their long-term significance is currently unknown.

In conclusion, there is currently not enough information to characterise the potential benefit risk balance of mecasermin rinfabate, especially when compared to rhIGF-I alone, for which much more data are available.