

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-839**

**Medical Review(s)**

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

**Date:** Tuesday, August 30, 2005  
**NDA:** 21-839  
**Sponsor:** Tercica, INC.  
**Proprietary Name:** Increlex (mecasermin [rNDA origin]) injection  
**Review designation:** Priority Review  
**Author:** Robert J. Meyer, MD, Director, ODE II

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**Introduction:** This is the decisional memorandum for the approval action for Increlex (mecasermin) for the long-term treatment of growth failure in children with severe, primary IGF-1 deficiency or those with growth hormone (GH) gene deletion, whose immune systems would otherwise then view GH as a foreign protein, and hence have developed neutralizing GH antibodies.

Mecasermin is the established (USAN) name for recombinant human insulin-like growth factor-1 or IGF-1. The drug substance, which is produced by genetically modified *E. coli*, is a 70 amino acid protein. Mecasermin is completely homologous to native human IGF-1, which is the main affecter of growth resulting from GH secretion. The drug product is an aqueous solution intended for twice daily, subcutaneous injection in children with severe growth retardation and low IGF-1 despite exposure to endogenous or exogenous GH (including those with GH receptor defects, IGF-1 gene defects and children with absent GH who have developed neutralizing antibodies to exogenous GH).

The patient population for which this drug is intended is quite limited and, indeed, mecasermin carries an orphan designation for the treatment of growth hormone insensitivity syndrome (*as documented in a letter to Tercica from the Office of Orphan Product Development on September 16, 2004, acknowledging the transfer of the orphan designation to its new sponsor – see below*). These children, once diagnosed, are to be treated chronically with mecasermin until epiphyseal plate closure (i.e., until no further linear growth is possible). IGF-1, besides its effects in promoting linear growth, also has some homology to the insulin molecule and is active at the insulin receptor, albeit to a lesser degree than insulin itself. IGF-1, then, is involved in glucose metabolism and therapy with IGF-1 is pharmacologically predicted to lead to hypoglycemia as one of its consequences. Additionally, since exogenous GH exerts much of its growth effects via IGF-1, some of the well-characterized safety issues with GH used in children (such as acromegalic changes, joint/bone pain and others) may be potentially seen with IGF-1 administration itself.

Laron's syndrome consists of well-characterized mutations in the growth hormone receptor and is amongst the primary targets of this drug's indication and its development. These children do not grow, as the GH they produce is ineffective at producing the normal, subsequent physiologic

responses because of the GH receptor abnormalities. Laron's syndrome is very rare, with the total number of known affected individuals being below 500 patients (approximately 350) and the extended population encompassed by the indication of only several thousand more affected individuals. Despite this, the NDA consists of results from 71 patients, with a total exposure of 274 patient-years with a mean duration of treatment of 3.9 years per patient. The large majority of the patients in the clinical program were Laron patients, who have well-characterized growth retardation, allowing for the successful use of historical controls. This patient exposure data is very generous considering the rarity of Laron's and even the related diseases and syndrome that comprise severe IGF-1 deficiency.

This application is sponsored by Tercica, who obtained the rights to development and to the submission from Genentech, the original developer of Increlex. The NDA was received on February 28<sup>th</sup>, 2005, and the application was granted a priority review as the intended use population has no currently approved alternative treatment. Late in the review of NDA 21-839, a Citizen Petition (CP) was submitted by Insmad, the sponsor of an IGF-1 product that also contains a second recombinant molecule (the IGF binding protein-3) that is naturally present in humans and to which IGF substantially binds in vivo, so that the IGF-1 in the circulation is primarily bound to this IGFBP-3 (whether that IGFBP-3 is native or exogenous). In that CP, Insmad is asking the agency to deny approval of NDA 21-839. This memo will later address this CP.

**CMC:** The primary CMC review was done by Dr. Ysern of ONDC, with Dr. Moore as the secondary reviewer.

As noted above, this drug substance is produced via recombinant DNA technology in *E. coli*. The protein itself is fairly simple, being a monomeric, non-glycosylated, 70 amino acid protein with 3 internal disulfide bonds. As previously mentioned, its sequence is identical to normal native human IGF-1. The drug substance is produced by

with the bulk then being shipped to Baxter Pharmaceutical Solutions in Bloomington, IN where it is made into a 10 mg/ml aqueous solution via standard

processes. The microbiologic consult found these production methods to be acceptable for this sterile, injectable product.

The CMC review has found the methods of manufacture of the clinical lots and those to be marketed to be satisfactory for approval purposes and there are no significant issues with changes in the formulation or production of the product leading to any questions about the applicability of the clinical findings to the treatment results with the marketed product. There are some post-approval agreements that Tercica has committed to that address some residual minor CMC concerns (e.g., fortifying the data on stability in certain presentations and conditions), but the CMC reviews recommend approval from their perspective.

**Pharm/Tox:** The primary reviewer on this application was Dr. Xiao, with Dr. El-Hage as secondary reviewer.

Most of the notable toxicity/toxicology of mecasermin is directly related to its known and expected pharmacology and that which was observed was shown to be reversible. In the animal

toxicology studies, dosing was limited by the occurrence of hypoglycemia, though substantial multiples of human dosing were still achieved. The only histological change of note in chronic toxicity studies (where increased weight, hypoglycemia and organomegaly were prominent), was in the thymus in rats, where there was an increase in the cortex size and, in dogs, where adrenal medullary fibrosis was seen.

In the reprotoxicity studies, there was no sign of teratogenicity at the doses studied (limited by maternal toxicity, but still in reasonable multiples to human exposure) and fertility was only decreased at 5 times the expected exposure in human use. All genotoxicity studies were negative. The carcinogenicity findings consisted of keratoacanthomas (males), pheochromocytomas (males and females), and mammary tumors (males). These findings were considered drug-related in the 2-year rat carcinogenicity study. All of these occurred at levels of exposure that exceeded the maximum tolerated dose (MTD) and well exceeding expected human exposure. Since mecasermin is an endogenous hormone for an orphan indication and is non-genotoxic, this rat study is considered sufficient (i.e., without a second species). The Pharm/Tox team is also recommending approval from their perspective and is not recommending further studies.

**Clinical Pharmacology:** The primary OCPB reviewer was Dr. Sang Chung, with Dr. Ahn as the secondary reviewer.

This drug, which is an aqueous solution, is given subcutaneously in divided doses (twice daily). It should be noted that administration early in the development was attempted intravenously, but this route proved to be poorly tolerated and toxic (including the induction of syncope). The proposed dosing (0.08 – 0.12 mg/kg BID subcutaneously) was chosen based on attempting to normalize levels of IGF-1. Additionally, while doses of 0.06 mg/kg were effective, they only showed marginal growth effects compared to 0.08 and 0.12 mg/kg per twice daily dose.

Given subcutaneously, it appears that the bioavailability of mecasermin approaches 100%. The T<sub>max</sub> occurs within 2 to 3 hours and the terminal half-life is in the range of 4 to more than 24 hours (depending on the population), with an average in patients of 5.8 hours. The sponsor's data show that for serum AUCs, the drug has less than dose-proportional rises in exposure as doses increase. Clearance appears more rapid in severe IGF deficient patients, perhaps related to this population having demonstrated lower IGF binding protein-3 levels, as there is also a demonstrated inverse relationship between IGFBP-3 levels and clearance. No metabolites of mecasermin have been identified. Both the liver and kidneys can metabolize IGF-1 and animal studies suggest the kidneys are largely responsible for its elimination.

The OCPB team is recommending approval without need for further studies

**Clinical/Statistical:** The primary medical officer on this application is Dr. Dragos Roman, with Dr. Orloff as secondary. The primary statistical review was by Dr. Todd Sahlroot, with Dr. Nevius as the secondary reviewer.

As previously mentioned, the intended patient population for the indication is quite limited (children with severe, primary IGF-1 deficiency (IGFD) or with growth hormone (GH) gene

deletion and neutralizing GH antibodies), particularly the Laron syndrome patients. The definition of severe IGFD used for the purposes of the labeling is an SD score for height less than  $\bar{3}$ , an SD score for serum IGF-1 levels of less than  $\bar{3}$  and normal or elevated GH level.

The total number of patients reported in this NDA who have at least some drug exposure was 71 patients, with a total of 274 patient-years of treatment with a mean duration of exposure of 3.85 years. Fifty three of these patients had Laron's syndrome. Since there are only estimated to be 350 patients world-wide with this disorder, the sponsor studied an impressive proportion of those patients. The entire population for whom this drug would be indicated (all IGFD patients and GH unresponsive children due to neutralizing antibodies) is only estimated to be in the thousands. The large majority of these data are open-label, without comparators, representing data pooled from several small trials (3, one of which was a controlled study), open-label follow-on treatment from these studies and a relatively large and long investigator trial. This data set is quite acceptable, given the rare, orphan indication. The extent of the data and the number of patients studied relative to the existing affected population in many ways exceeds what might otherwise be expected in such a case, given the prior experience of DMEDP and the ODE<sup>1</sup>.

It must be emphasized that the reason most of these data are uncontrolled is largely driven by ethical considerations (giving long-term placebo to patients where the test therapy itself is targeted to correct a well-understood pathophysiologic mechanism). However, since the growth of such children is reasonably well characterized, the use of historical controls for efficacy is feasible. Because Laron's syndrome is accompanied by pathology beyond simple growth retardation, the safety assessments are a bit more difficult with the lack of comparator, but this does not mean safety issues will be missed so much as it means that things may be ascribed as possibly related to mecaseprin therapy that in fact are not causally related. Finally, it should be noted that, while much of the sponsor's data comes from patients with Laron's, there is no reason to believe that the efficacy data and safety data would not be extrapolatable to the broader population. If anything, due to their other dysmorphisms, Laron's patients arguably may be a more sensitive population in terms of safety, as likely or more to suffer any ill effects from mecaseprin exposure compared to the broader population of severe IGF-1 deficient patients.

*Efficacy:* The data submitted by Tercica shows a statistically significant acceleration of linear growth (as characterized by height velocity or HV) compared to baseline HV assessments, with the mean HV increasing at one year's treatment by 5.2 cm/yr (mean baseline of  $2.8 \pm 1.8$  cm/year, 1 year mean of  $8.0 \pm 2.2$  cm/year). The mean HVs were also significantly increased in years 2 – 6. HV standard deviation scores (SDS) followed the same pattern, increasing from the mean at baseline of  $\bar{3}$  to an average at one year of  $+1.9$ . The large majority of patients showed a treatment effect in growth velocity, with only five patients having a HV of  $< 5$  cm/yr. Of these, one appeared to have a compliance issue, one had apparent concomitant poor nutrition. The three remaining still showed an increase in their HV SDS (by 1, 1.3 and 2), but this was less vigorous than the rest of the treated population.

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<sup>1</sup> A recent example: NDA 21,232 was for nitisinone, a drug to treat hereditary tyrosinemia, which is a rare disorder, but comparatively more common than Laron's syndrome. This NDA also was based on uncontrolled clinical data. In this case, there were 207 patients reported in NDA 21,232 for a disease with an incidence of about 1 in 100,000 live births, or about 40 patients born with HT each year in the US alone.

The major secondary analysis was the assessment of change in height SDS and this too showed a treatment effect, with mean height SD scores rising from  $6.7 \pm 1.8$  at baseline to a mean of  $5.9 \pm 1.8$  at 1 year. These elevations in height SDS were maintained through year 8 in those patients assessed out to that time period.

Bone age, relative to chronologic age, was also assessed in 49 patients, as a disproportional acceleration of bone age (and specifically epiphyseal closure) could lessen the eventual height reached, even if the drug was otherwise effective at accelerating growth. However, radiographically assessed mean bone age advanced only marginally above chronologic age (5.3 years mean vs. 4.9 years mean, respectively). Further, of the Laron's patients who were felt to be close to their adult height, all exceeded the mean height of untreated Laron's patients, suggesting the net effect is positive for the use of mecasermin in such patients.

An issue that impacts efficacy and, to a lesser extent, safety is antibody formation. It should be remembered that the patients studied in this program (and indicated in the labeling) have native IGF-1, but in very low quantity. Their immune systems, therefore, should not perceive mecasermin as a totally novel protein. Still, the development of antibodies to exogenous protein is an important assessment in any program of this sort. Antibody formation was assessed by an ELISA assay in four of the reported studies. Half of those assessed (i.e., 11 of 22) had anti-mecasermin antibodies reported at a least one time point in the first year of therapy. Titers do not appear to continue to increase with continued therapy, as supported from data from the follow-on study. The mean height velocity of the children with antibodies did not differ from those without (mean of 7.9 vs. 7.3 cm/yr respectively). There is no evidence, then, that these antibodies are neutralizing in their effect. There is also no evidence from the clinical program of a sensitizing effect in terms of hypersensitivity reactions.

*Safety:* The major adverse effects of mecasermin are pharmacologically predictable, particularly hypoglycemia. Overall, the safety experience from the 274 patient-years of drug use/exposure support the finding of a favorable risk-benefit balance, particularly given the lack of alternative treatment for the indicated, severely-affected population.

There were no deaths reported in the safety database. There were a total of 9 serious adverse events reported in the total database from the severe IGFD studies (including those from the 120-day safety update); of these, 5 were deemed "possibly related" by investigators. These events included two patients with seizures (one thought associated with hypoglycemia), a case of tonsillar hypertrophy needing excision (note that there were 7 total patients who had tonsillectomies, but only this one was reported as an SAE), a case of renal stones, a case of papilloedema and a case of tricuspid insufficiency and RVH noted by echocardiogram (without apparent clinical correlates). The study experience of mecasermin in diabetes mellitus (DM) and in mixed etiology short stature (idiopathic, Laron's, GH gene deletion) syndrome added some cases of SAEs, including a hypoglycemia in the DM trials and a case of sleep apnea with resultant cardiomegaly and two cases with elevated LFTs, one that showed a positive response to rechallenge.

As stated above, there are AEs that would be predicted pharmacologically (specifically hypoglycemia) and/or that have been seen with chronic GH administration and may then be

mediated by IGF-1. These occurrences include pseudotumor cerebri, slipped capital femoral epiphyses and arthralgias/myalgias. It is notable that no patient was reported to have withdrawn from the clinical studies because of adverse events.

Forty-two percent of patients reported at least one hypoglycemic episode during their therapy. Of these, only 11% were deemed to be severe and 24% of all the episodes were reported in the first year of treatment. There were four seizures reported related to hypoglycemia. The occurrence of hypoglycemia is reported to be related to the degree of short stature (more likely with more severe growth retardation), age (more likely in young patients) and those with prior hypoglycemia by history (*NOTE: close to half of all patients with hypoglycemia on treatment had reported such episodes prior to treatment*). The sponsor is recommending a titration of dosing, starting at 0.04 – 0.08 mg/kg given BID, increasing to 0.08 to 0.12 mg/kg if tolerated for at least 1 week (i.e., no hypoglycemia). To alleviate this risk, the sponsor is recommending taking the drug with meals (within 30 minutes) and withholding the drug if the patient cannot eat or otherwise time the injection to a meal. This seems reasonable and should help obviate this concern.

Data from this program and the DM program for mecasermin suggest that treatment may be causally associated with tonsillar and adenoid hypertrophy, which can then result in secondary complications, such as snoring/obstructive sleep apnea and chronic otitis media. This can be monitored and treated surgically, if indicated. Since it can be monitored, however, this should not be a grounds for non-approval, though this possible AE deserves mention in the appropriate sections of the labeling.

There are some findings from laboratory and other routine examinations (echocardiograms) that, due to the uncontrolled nature of most of the safety data, are a bit hard to definitively interpret.

As for the laboratory data, the most notable findings are some transient elevations in ASTs and LDHs in some individuals, occasionally accompanied by ALT elevations (but not with substantial bilirubin rises). Many of these patients had abnormalities prior to treatment in at least one of these parameters and no patient had to stop treatment due to the increase in these enzymes.

Echocardiograms were assessed in 33 patients. Three of these had baseline abnormalities that reportedly reversed on treatment. Of the other thirty, 16 had normal examinations throughout treatment, 9 had transient findings and 5 had abnormalities that were not shown to be transient. These latter cases included mitral valve prolapse, an ASD due to a patent foramen ovale, a case of tricuspid insufficiency and two cases of LV hypertrophy. Such findings without a control group can neither be confidently excluded from causality nor confirmed, but it is notable that chronic GH replacement therapy (which raises endogenous IGF) is not known to cause cardiac changes of consequence. These occurrences deserve some mention in labeling, but as none had significant clinical correlates and because of uncertainty causality (and it appears unlikely MVP or an ASD would be in any way related and other reported changes such as tricuspid insufficiency could be secondarily related due to effects on sleep breathing and airways), these findings certainly do not form not sufficient grounds to not approve the drug.

One other routine examination worth noting is abdominal ultrasounds, done to assess organ growth. It appears that organ growth of the spleen and kidneys follows linear growth in many ways with fairly rapid and noticeable growth with the initial months of treatment, subsequently slowing down. Very few patients experienced enlargements out of normal range and none was associated with disease (renal function was normal in these patients).

Three patients developed clinically important increased intracranial pressures (without anatomic obstruction), one of whom needed a lumbar puncture to decompress, but none interrupted treatment – so the process resolved without cessation of therapy. This effect has been seen with and is labeled for the growth hormone products and again should be handled in labeling, as it is for growth hormone.

In conclusion, the safety of mecasermin has been reasonably studied (particularly in light of the very limited target population). With proper labeling and with the understanding that this drug will be prescribed by physicians with high levels of expertise and experience in growth issues, mecasermin is sufficiently safe for approval for the indicated population.

**NOTE on the Citizen Petition of Aug. 10<sup>th</sup>, 2005:** Late in the review cycle for this priority approval drug, the Agency received a citizen petition from Insmmed, the maker of the mecasermin/IGFBP-3 product. It asks the Agency not to approve NDA 21-839 based on several of the following points:

- There is an inadequate safety database, based largely on a retrospective analysis of data from open-label treatment protocols (“compassionate use”).
- Hypoglycemia specifically related to free IGF-1 administration
- Tercica’s investigators were not adequately trained in conducting, monitoring or data collection in clinical trials and the data is therefore of suspect quality.
- There is insufficient safety data on the use of mecasermin in severe primary IGFD

Therefore, Insmmed asserts, FDA must not approve Increlex.

As the signatory authority for this application, I find these arguments, which are not based on procedural or legal matters, but on matters of medical judgment, to be less than compelling. As mentioned previously in this document, the amount of data (safety and efficacy) for this drug is very large in proportion to the target population for the indication, which is likely in the range of 10,000 patients at most. Having over 250 patient-years experience means that the patient years of experience exceeds or is certainly comparable to that of most routine NDAs, proportionate to the size of the target population. For instance, a very generously sized HMG CoA-reductase inhibitor program may have data collected on 10,000 patients (controlled and uncontrolled) but the target population may be 10 to 20 million patients.

The source of the data (three clinical trials (limited in size), an extension trial and an investigator trial) is not at all atypical for an orphan indication, particularly one with a very limited patient population. For instance, therapies for metabolic deficiency syndromes with similar sized populations have been approved based entirely on compassionate use experience. Ammonul a drug to treat disorders of the urea cycle (NDA 20-645 – approval date February 17, 2005) is a

recent example of such. This was approved based on clinical data from approximately 300 patients, many of whom did not follow a strict protocol. In very rare orphan indications where there are ethical constraints on withholding treatment, large multicenter randomized trials would be the clear exception, not the rule. Compared to other experience in this office with orphan drugs for rare conditions, the data base from Tercica is quite robust, in terms of quantity and quality. The early studies done by Genentech (Studies F0375, F0632, and F0671) had comprehensive protocols and the sponsor monitored the investigator-sponsored study. While the investigators who provided the clinical data to NDA 21-839 at individual sites around the world may not be investigators who routinely perform clinical trials, FDA found no reasons to doubt the veracity or the quality of the data provided. By definition, patients with Laron's syndrome are only treated by pediatric endocrinologists for whom growth disorders are a significant component of their clinical experience. They are experienced in the clinical management (including collecting relevant assessments) of such patients. Therefore, I believe Insmed's contention of poor data quality is not borne out in the FDA review. Insmed states that the database represented a retrospective analysis of data from open-label treatment protocols. It must be understood that the large majority of safety data reviewed by FDA for NDAs is not based on formal hypothesis testing and therefore the safety information on which we base our approval decisions routinely can be considered "retrospective" analyses. In this respect, the safety data for Tercica's mecaseimerin is by no means the exception.

As for the sufficiency of data for patients with other causes of severe IGFD beyond Laron's (those with very low IGF-1 levels, severe growth retardation and normal or high GH of other causes beyond defects of the GH receptor), we have no reason to believe that the data from the Laron's patients would not be generalizable to this broader population. Since Laron's patients have abnormalities in their physiology beyond linear growth alone that may well be more severe than those of others in the extended population, it is reasonable to believe that the Laron's patients would be an appropriately sensitive population to study mecaseimerin in. For hypoglycemia specifically, I know of no scientific basis to believe that the patients studied and presented in NDA 21-839 would have less sensitivity to the effects of mecaseimerin than others. Also, Insmed makes much of a change in the indication on the part of Tercica over the years of development (from growth hormone insensitivity syndrome to severe IGF deficiency). But much of this argument is semantic and not substantive. Tercica does not appear to be trying to "expand" the indicated population, so much as to use more precise language in light of evolving knowledge of the underlying pathophysiology of the various contributors to the IGFD/GHIS syndrome.

Finally, as to the point that there is an excessive risk of hypoglycemia specifically related to free IGF-1 administration, after review of the relatively robust database Tercica provided for mecaseimerin, I believe the risks of hypoglycemia have been adequately characterized for the purposes of labeling and approval. While hypoglycemia is clearly a risk with this product, I believe that the risk is outweighed by the benefits and can be alleviated (though likely not fully prevented) by dose titration at initiation and by carefully adhering to recommendations on timing the dosing of this drug to the intake of a meal ( $\pm$  30 minutes).

In short, Insmed's citizen petition raises many issues which we either explicitly or implicitly considered in reviewing NDA 21-839. In reviewing the entire package of reviews (clinical,

statistical, preclinical, clinical pharmacology, CMC, microbiology, etc.), I have concluded that Tercica has provided adequate evidence of safety and effectiveness for their product to allow it to be approved and adequately labeled such that patients and their families may use this with sufficient safety when under the guidance and care of a practiced physician.

(Note: Insmmed's August 25, 2005 letter to Dr. Orloff, and its attachment, address a number of issues concerning the comparative safety of Increlex and Insmmed's mecasermin/IGFBP-3 product. Most of these considerations relate to the scope and effect of any orphan exclusivity granted to Increlex, an issue the agency need not resolve at this juncture.)

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## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-839  
Submission Code N 000

Letter Date 24 February 2005

Stamp Date N/A (electronic submission)  
PDUFA Goal Date August 31, 2005

Reviewer Name Dragos Roman  
Review Completion Date July 29, 2005

Established Name mecasemin  
(Proposed) Trade Name INCRELEX  
Therapeutic Class Recombinant Human Insulin-like Growth  
Factor-I  
Applicant Tercica Inc.

Priority Designation P

Formulation injectable  
Dosing Regimen 80-120 µg/kg twice a day as a subcutaneous  
bolus injection

Indication  1

**Intended Population**  
(Primary IGFD).

Children with primary IGF-1 deficiency

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Clinical Review  
{Dragos Roman}  
{21-839/N 000}  
{Increlex (mecasermin)}

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

From a clinical perspective, mecasermin should be approved as replacement therapy for the orphan indication of severe short stature in (1) patients with primary IGF-I deficiency and (2) patients with growth hormone gene deletion and neutralizing antibodies to growth hormone (GH).

Accepting the limitations of a baseline-controlled clinical trial and the fact that a placebo-control clinical trial is unethical and cannot be conducted in severe primary IGFD, and taking into consideration the extreme short stature observed in primary IGFD, mecasermin has an acceptable benefit-to-risk profile for the proposed indication if used according to the label. Mecasermin treatment was effective in increasing linear growth in patients with severe primary IGFD at to-be-marketed doses of 80-120 µg/kg BID.<sup>1</sup> The adverse event profile of mecasermin, judged within the limits of a clinical trial without a comparator cohort for the safety observations, is consistent with that published in the medical literature to date and with IGF-I's known mechanisms of action (insulin-like activity and main mediator of GH's action). Several safety observations made in the clinical trials related to laboratory abnormalities (including liver enzyme elevations), ultrasonographic (including echocardiographic) findings do not have in general clear clinical correlates and cannot be differentiated from either background illnesses/adverse events or from clinical features related to Laron Syndrome itself. In general there are no major differences between this reviewer's and applicant's efficacy and safety conclusions.

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<sup>1</sup> BID = twice a day.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The applicant should propose a plan that addresses the potential off-label use of mecasermin as an anabolic agent.

### 1.2.2 Required Phase 4 Commitments

None.

### 1.2.3 Other Phase 4 Requests

None.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Mecasermin is human insulin-like growth factor-1 (rhIGF-1).<sup>2</sup> IGF-I is the main mediator of growth hormone's physiological actions including those related to linear growth. In addition, as it is structurally related to insulin, IGF-I binds the insulin receptor and mimics many of the effects of insulin including its ability to induce hypoglycemia.<sup>3</sup> Deficiencies in GH and IGF-I production result in severe short stature. Most patients with short stature are treated successfully with somatropin (human recombinant GH), an approved drug product that has been used in children (and adults) for approximately four decades. However, a subset of patients with short stature is resistant to GH despite adequate or even excessive GH production. This GH resistance is generally

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<sup>2</sup> Mecasermin is a synthetic version of the native, 70 amino acid, single chain, IGF-I protein. Like endogenous IGF-I, mecasermin is not glycosylated and contains three intramolecular disulfide bridges. Its molecular weight is 7649 daltons. Mecasermin is synthesized in an E.coli vector by recombinant DNA technology, subsequently purified and finally formulated as a 10 mg/ml sterile solution in a 5 ml vial for subcutaneous injection.

<sup>3</sup> The hypoglycemic potency of IGF-I in humans is  $\leq 10\%$  of that of insulin.

due to GH receptor mutations or mutations in the postreceptor signaling pathways. It is for this patient population that mecasermin has been developed, the rationale being that it bypasses the metabolic defect responsible for GH resistance.<sup>4</sup>

The proposed indication for mecasermin is long-term treatment of growth failure in children with primary IGF-I deficiency<sup>5</sup> and children with GH gene deletion.<sup>6</sup> The target population is estimated between 350 patients (Laron Syndrome) and several thousands for the “extended” indication (see footnote 4). Primary IGFD is an orphan disease.

Mecasermin is a new molecular entity. Due to its potential hypoglycemic effect it is to be administered with meals. It is given as a subcutaneous injection twice a day at a dose of 80-120 µg/kg. As is the case with GH, mecasermin treatment is to be initiated in early childhood and continued up to the point of epiphysial closure.

Mecasermin has been studied in 71 patients with primary IGFD for a total exposure of 274 patient-years.<sup>7</sup> The mecasermin clinical program consisted initially of three small clinical trials which enrolled between 6-8 patients each and lasted between 1-2 years. Patients from these trials were rolled into an open-label clinical trial for two additional years and subsequently into an investigator trial which enrolled 48 additional treatment-naïve patients.<sup>8</sup> Individual patient exposures to mecasermin in the primary IGFD clinical

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<sup>4</sup> Several clinical terms have been used to describe these patients: growth hormone resistance, GH insensitivity syndrome (GHIS), primary IGF-I deficiency (primary IGFD). Within this syndromes some individual conditions are well characterized such as GH receptor mutations (Laron Syndrome), postreceptor defects, IGF-I gene deletions, and neutralizing antibodies to GH. The short stature in children with primary IGFD is profound (adult height ranges between -12 and -3 SD score; average adult height is 3.5’).

<sup>5</sup> This is further and specifically characterized by (1) a height standard deviation score that is less than or equal to -3.0, (2) a basal IGF-1 standard deviation score less than or equal to -3.0, and (3) normal or elevated growth hormone level.

<sup>6</sup> Patients with GH gene deletion respond initially to GH but subsequently developed neutralizing antibodies to exogenously administered GH, which render GH treatment ineffective.

<sup>7</sup> The mean duration of mecasermin treatment was  $3.9 \pm 3.2$  years (median duration of treatment: 3 years).

<sup>8</sup> Mecasermin has been initially developed by Genentech who discontinued the mecasermin clinical program in 1997 “for reasons unrelated to the effects of rhIGF-I [...] in children with primary IGFD.” In 2002 Tercia Inc. acquired

program extend up to and beyond 10 years. With the exception of one of the small initial trials (placebo-controlled, crossover design, 6 months duration, conducted in 8 patients) the entire clinical trial program consists in open label, baseline-controlled clinical trials. The efficacy and safety analyses integrate the clinical data from all the mecasermin clinical trials.<sup>9</sup> The major limitation of the mecasermin clinical trials is the absence of a control group, which makes an accurate interpretation of the incidence of adverse events difficult. This, however, is not necessarily a shortcoming of the clinical program; it is rather a consequence of the fact that conducting a placebo-controlled clinical trial of rhIGF-I would be unethical once rhIGF-I has been proven to increase height in this patient population.<sup>10</sup>

### 1.3.2 Efficacy

The effectiveness of mecasermin in primary IGFD has been evaluated in a series of analyses conducted with efficacy data pooled from 5 Phase II/III clinical trials. The primary efficacy analysis was a comparison of height velocity for every year on-treatment (up to 8 years) with the pre-treatment height velocity. The secondary analysis compared height SDS<sup>11</sup> for every year on-treatment with baseline height SDS. The efficacy endpoints and the efficacy analyses are standard for statural clinical trials.

Of the 71 patients enrolled across the 5 clinical studies, 58 subjects had pre-treatment and first year height velocity data and were included in the primary efficacy analysis; 61

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Genentech's intellectual property rights, data, and manufacturing process.

<sup>9</sup> In addition to patients with primary IGFD, mecasermin has been administered in multiple studies to a variety of patient populations (mostly adult) including Type 1 diabetes (> 500 subjects), Type 2 diabetes (> 700 subjects), and HIV cachexia (11 subjects). Approximately 200 healthy volunteers and subjects with Type 1 and Type 2 DM participated in bioequivalence and clinical pharmacology studies of mecasermin.

<sup>10</sup> From an efficacy standpoint it is important to recognize that the natural course of this condition is relatively well characterized. Growth charts specific for patients with Laron Syndrome are currently available and patients with primary IGFD, if appropriately diagnosed, are not anticipated to exhibit spontaneous correction of their growth deficits. The consequence of this observation is that growth acceleration on mecasermin is drug-related.

<sup>11</sup> Height SD score or height SDS is height standard deviation score.

patients had baseline and first year height measurements and were included in the secondary analysis.<sup>12</sup>

### Primary analysis

Mecasermin administration resulted in a statistically significant increase in height velocity (HV) for up to 6 years of treatment when compared to baseline HV. The mean  $\pm$  SD height velocity (cm/yr) increased from  $2.8 \pm 1.8$  cm/yr at baseline to  $8.0 \pm 2.2$  cm/yr after one year of mecasermin treatment (range 1.8 to 12.8 cm/yr). This finding was statistically significant.<sup>13</sup> The height velocities for Year 2 through Year 6 (5.8, 5.5, 4.7, 4.7, and 4.8 cm/yr, respectively) were also statistically greater than baseline HV.<sup>14</sup> The mean yearly changes in height velocity (baseline subtracted) for Year 1 through Year 8 were  $5.2 \pm 2.6$ ,  $2.9 \pm 2.4$ ,  $2.3 \pm 2.4$ ,  $1.5 \pm 2.2$ ,  $1.5 \pm 1.8$ ,  $1.5 \pm 1.7$ ,  $1.0 \pm 2.1$ , and  $0.7 \pm 2.5$  cm.

The same analysis applied to height velocity SD score (HV SDS) yielded similar results; statistically significant improvements in HV SDS were observed for up to 7 years. The mean height velocity SD score at baseline was -3.3. Height velocity SD scores at Year 1 through Year 7 were:  $1.9 \pm 3.0$ ,  $-0.2 \pm 1.6$ ,  $-0.2 \pm 2.0$ ,  $-0.7 \pm 2.1$ ,  $-0.6 \pm 2.1$ ,  $-0.4 \pm 1.4$ , and  $-0.4 \pm 1.9$ , respectively. The mean yearly changes (baseline subtracted) in HV SDS for Year 1 through Year 8 were  $5.2 \pm 3.1$ ,  $3.1 \pm 2.3$ ,  $2.9 \pm 2.3$ ,  $2.2 \pm 2.2$ ,  $2.5 \pm 2.2$ ,  $2.7 \pm 1.7$ ,  $2.5 \pm 2.1$ , and  $2.7 \pm 2.8$ , respectively. The vast majority of patients responded to treatment.<sup>15</sup>

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<sup>12</sup> Ten patients had less than one year of efficacy data on trial and were excluded from the efficacy analysis.

<sup>13</sup> Paired t-test comparing height velocity for Year 1 to pre-treatment height velocity: p-value < 0.0001.

<sup>14</sup> Paired t-tests comparing height velocity for each year (Year 2 through Year 6) to pre-treatment height velocity were: p < 0.0001, < 0.0001, 0.0045, 0.0015, and 0.0009, respectively). The applicant reports "positive trends" for Years 7 and 8 (4.6 and 4.3 cm/yr, respectively) but the sample sizes were small (only 16 and 13 patients, respectively). As seen in other statural clinical trials there was gradual attrition of patients over time.

<sup>15</sup> Only five patients had HV < 5 cm/yr during the first year of treatment. One was, reportedly, non-compliant; another appears to have had concomitantly poor nutrition; the other three improved their height SDS long-term by 1, 1.3 and 2, respectively (see secondary analysis for mean SDS results).

## Secondary analysis

Mecasermin administration resulted in a statistically significant increase in height SDS for up to 8 years of treatment. The mean height SD score at baseline was  $-6.7 \pm 1.8$ , indicative of severe short stature; it increased to  $-5.9 \pm 1.8$  after one year of treatment ( $p < 0.0001$ ). The mean height SD scores for Year 2 through Year 8 ( $-5.6 \pm 1.8$ ,  $-5.4 \pm 1.8$ ,  $-5.5 \pm 1.9$ ,  $-5.6 \pm 1.8$ ,  $-5.4 \pm 1.8$ ,  $-5.2 \pm 2.0$ , and  $-5.2 \pm 2.0$ , respectively) reached all statistical significance when compared to baseline height SDS.<sup>16</sup> The height SDS changes relative to baseline that were observed on treatment were 0.8 (Year 1), 1.2 (Year 2), 1.4 (Year 3), 1.3 (Year 4), 1.4 (Years 5 through 7), and 1.5 (Year 8); most of the increase in height SDS was achieved by Year 3 and was maintained through Year 8.

Several sensitivity analyses of subjects who were not included in the primary analysis for a variety of reasons, indicate that the vast majority of them responded to mecaseimerin treatment.<sup>17</sup>

When given as a subcutaneous injection twice a day, mecaseimerin treatment induced a dose-response effect for doses of 60-120  $\mu\text{g}/\text{kg}$  (see Dose Regimen and Administration Section).<sup>18</sup>

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<sup>16</sup>  $p < 0.0001$ ,  $< 0.0001$ ,  $< 0.0001$ ,  $0.0001$ ,  $< 0.0001$ ,  $0.0001$ , and  $0.0003$ , respectively.

<sup>17</sup> Such analyses looked at patients without baseline HV data, subjects with data for less than one year, non-compliant patients, subjects lost for follow-up, and other subjects who discontinued before reaching near-adult heights.

<sup>18</sup> In Study F0632 a mecaseimerin regimen of 60  $\mu\text{g}/\text{kg}$  BID given over 12 months in 6 patients increased the mean growth rate from  $1.2 \pm 0.6$  cm/yr (range 0.45 to 2.0 cm/yr) at baseline to  $5.4 \pm 2.3$  cm/yr (range 2.4 to 8.4 cm/yr). In contrast, during Study 1419 a mecaseimerin dose regimen of 80-120  $\mu\text{g}/\text{kg}$  BID given to 51 patients increase height velocity from  $2.8 \pm 1.8$  cm/yr (range 0.0 to 7.7 cm/yr) at baseline to  $8.0 \pm 2.2$  cm/yr (range 1.8 to 12.8 cm/yr). In addition, the mean change in height velocity relative to baseline for the 60  $\mu\text{g}/\text{kg}$  BID (4.1 cm) was inferior to the to-be-marketed regimen ( $5.2 \pm 2.6$  cm) and was not associated with significant changes in height SDS and catch-up growth

Mecasermin treatment did not appear to be associated with an undue acceleration in bone age. Preliminary data collected in six subjects who reached near-adult heights indicate that their heights were greater than the mean height of a population of untreated children with Laron Syndrome and that the estimated height gain, albeit variable, can be substantial (mean: 16 cm; range 3 to 23 cm).<sup>19</sup> Low-titer anti-IGF-I antibodies were observed on at least one occasion in 11 of 22 subjects tested during the first year of treatment;<sup>20</sup> for this duration of treatment the mean height velocities were comparable between antibody-positive and antibody-negative patients.

In conclusion, mecasermin treatment was effective in increasing linear growth in patients with severe primary IGFD at doses of 80-120 µg/kg BID. Mecasermin more than doubled the mean height velocity in the first year of treatment and induced a distinct “catch-up” growth phenomenon. Although subsequently the mean HV decreased, it remained at levels above those present at baseline. Mean height SDS (which compares the patients’ heights to those of the general population across ages and gender) improved steadily for 3 years and was maintained for the next 5 years. Preliminary data in a few patients suggest that gains in final height can be substantial. When judged in the context of linear growth observed with other products (specifically GH), the growth associated with rhIGF-I (mecasermin) is slower than that observed in GH deficiency and comparable to that observed in idiopathic short stature during the first year of treatment.<sup>21</sup>

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<sup>19</sup> Three of the 6 patients who reached near-final height also received Lupron during puberty.

<sup>20</sup> Antibody titers did not increase during the second year of treatment.

<sup>21</sup> For idiopathic short stature the height velocity at one year is approximately 8-9 cm/yr (change from baseline 4-5 cm/yr) for doses of 0.24/0.37mg/kg/week (source: Humatrope review); for a dose of 0.3 mg/kg/week the one year HV was  $7.5 \pm 1.2$ cm/year and the baseline subtracted change was  $3.1 \pm 1.7$  cm/yr. (source: Nutropin review). One-year height velocity in patients with GH deficiency ranges between 7.5 and 13.5 cm/yr (average approximately 10 cm/yr) depending on the dose used (baseline subtracted change in HV is around 7-8 cm/yr)

### 1.3.3 Safety

It is important to recognize from the beginning that there is no comparator group against which the incidence of adverse events collected in the primary IGFD clinical program can be evaluated.<sup>22</sup> In addition, Laron Syndrome<sup>23</sup> itself is not simply a condition of severe short stature; it has a complex physical and metabolic picture with multiple biochemical and structural abnormalities, some of which may not be fully understood or characterized. Finally, the mecasermin primary IGFD clinical program is relatively heterogeneous with respect to the safety variables evaluated, as the frequency and the type of safety assessments differed to some extent between studies and even within the same study. Therefore, in drawing final safety conclusions one has to rely on a combination of observations including the frequency and severity of the safety findings, the information already available from the use of GH for other indications (since IGF-I is GH's major mediator and the clinical experience with GH is extensive) and to a lesser extent the placebo-controlled mecasermin clinical trials conducted in pediatric patients for other indications investigational. Due to the absence of a comparator group this safety review will present the safety information descriptively and will follow a somewhat didactic presentation that will include patient deaths, serious adverse events (SAEs), patient withdrawals from the clinical trials due to adverse events, frequent treatment-emergent adverse events (TEAEs), adverse events (AEs) of special interest, and clinical laboratory findings. Similarities with the known adverse profile of GH and the already described abnormalities in Laron Syndrome will be highlighted during the summary. Emphasis is placed on both positive and negative findings.

#### **Deaths**

There were no patient deaths in the primary IGFD clinical development program.

#### **Serious adverse events**

Six serious adverse events (SAEs) were initially recorded in the primary IGFD program. Of these, two SAEs were deemed "possibly related" to mecasermin by the investigators. They were tonsillar hypertrophy (which subsequently required adenotonsillectomy) and moderately severe tricuspid insufficiency associated with right ventricular hypertrophy.<sup>24</sup> A third SAE (judged "possibly unrelated") was a seizure that may have been associated with hypoglycemia. Three additional "possibly related" SAEs (loss of consciousness/seizure-like activity, renal calculus and papilledema/headache/Arnold-Chiari malformation) were added with the 120-day safety update.

In the mecasermin type 1 diabetes program, SAEs that were deemed drug-related in children were hypoglycemia and progression of retinopathy (one patient each). In investigator sponsored studies of mecasermin for the treatment of short stature, SAEs deemed related or possibly related to study drug were sleep apnea/ pulmonary hypertension/ cardiomegaly (one patient with Laron

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<sup>22</sup> In essence, the primary IGFD clinical program included single- and multicenter, baseline-controlled, open-label clinical trials.

<sup>23</sup> Sixty-one out of the 71 patients (86 %) who participated in the primary IGFD program had Laron Syndrome.

<sup>24</sup> This diagnosis was made echocardiographically and was not associated with any clinical manifestations.

syndrome) and liver enzyme elevation (in two patients: one with GH deletion and one with non-growth deficient short stature; in one of them the liver enzyme elevation recurred on re-challenge with the study drug).<sup>25</sup>

### **Withdrawals from the clinical trials due to adverse events**

There were no clinical trial withdrawals due to adverse events.<sup>26</sup> The only adverse event that required on-trial dose reduction in a few patients was hypoglycemia.

### **Treatment-emergent adverse events**

Forty-eight (68%) patients reported at least one adverse event during the clinical trial. The most frequent treatment-emergent adverse events (TEAEs) were hypoglycemia,<sup>27</sup> injection site hypertrophy,<sup>28</sup> and headache.<sup>29</sup> Other TEAEs that occurred in  $\geq 10\%$  of patients were URI, snoring, hypoacusis, pyrexia, vomiting, otitis media, tonsillar hypertrophy, cough, nasopharyngitis, tooth caries, thymus hypertrophy, fluid in middle ear, arthralgia, pain in extremity, influenza, ear tube insertion, dry skin, cardiac murmurs, and nasal congestion.

Some frequently encountered TEAEs were clearly associated with the study drug (e.g. injection site reactions, hypoglycemia). Others were signs, symptoms, or conditions commonly seen in any pediatric population (e.g. upper respiratory infection, pyrexia, vomiting, otitis media, influenza, etc). A third group represents adverse events that can be seen in children in general but are at the same time symptoms/conditions that can be mechanistically associated with IGF-1 (e.g. snoring, hypoacusis, otitis media, tonsillar hypertrophy, thymus hypertrophy, arthralgia, convulsions, gynecomastia). The absence

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<sup>25</sup> Of significance is also the fact that intravenous (i.v.) administration of mecasermin has been associated with severe vasovagal reaction and syncope (associated with bradycardia and brief asystole) and generalized tonic-clonic seizures in healthy volunteers (one subject each); subsequent to these events the i.v. route of administration has been discontinued.

<sup>26</sup> Of the 71 patients enrolled, eleven discontinued early: four (5.6 %) for non-compliance, 1 (1.4 %) for parent/subject decision, 1 (1.4 %) for poor growth, and 5 (7%) were lost for follow-up.

<sup>27</sup> 30 patients or 42 %; in all but one patient hypoglycemia was considered treatment-related.

<sup>28</sup> 21 patients or 30% (in all patients considered treatment-related). Injection site hypertrophy or lipohypertrophy was described in general as "mild" in intensity, occasionally "moderate" and only in one case "severe." Reportedly, it was associated with lack of proper rotation of the injection sites. In addition to "hypertrophy," other adverse events associated with injections were injection site bruising (5 patients or 7%) and injection site pain (2 patients or 3%).

<sup>29</sup> 20 patients or 28%; in about 2/3 patients considered treatment related.

of a comparator or of background adverse event rates makes further interpretation difficult.

### Adverse events of special interest

Several adverse events and special assessments received particular attention during the clinical trials and are discussed next. They include hypoglycemia, lymphoid tissue hypertrophy, pseudotumor cerebri, retinopathy, and evaluations of organ growth.

The occurrence of hypoglycemia during mecasermin treatment is not an unexpected finding given the known insulinomimetic effect of IGF-I. Fifty percent of all hypoglycemic episodes were described as mild, 38% as moderate, and only 11% as severe.<sup>30</sup> Four hypoglycemic seizures have been associated with hypoglycemia. The risk of hypoglycemia appears to be correlated with the degree of short stature, young age and prior history of hypoglycemia.<sup>31</sup> The applicant proposes that initial mecasermin titration, occasional dose reduction, and careful dietary instructions<sup>32</sup> are likely to reduce the incidence of symptomatic hypoglycemia.

A relatively large proportion of patients reported TEAEs related to lymphoid tissue hypertrophy such as snoring, tonsillar hypertrophy, tonsillectomy/adenoidectomy, sleep apnea, middle ear effusion, otitis media. Although interpretation of such descriptive data is made difficult by the absence of a control group, it suggests that mecasermin treatment may be associated with hypertrophy of the adenotonsillar tissues and

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<sup>30</sup> Hypoglycemia was reported more frequently at the beginning of the mecasermin treatment (in 18% of patients during the first month and between 0 % and 6.6 % for the subsequent months in the first year of treatment). Overall, 24% of all episodes occurred over the first year of treatment.

<sup>31</sup> Approximately half of patients who experienced hypoglycemia on trial had a history of hypoglycemia.

<sup>32</sup> Dietary instructions refer to regular ingestion of a meal at the time of the mecasermin injection with special attention paid to small children who tend to eat more erratically.

secondary complications such as chronic middle ear effusions (and need for fluid drainage), hearing loss, sleep apnea.<sup>33</sup>

Not unexpectedly, a few patients (4%) developed pseudotumor cerebri. The condition resolved without treatment discontinuation (one patient had a decompression LP). Other adverse events known to occur in association with GH that were observed in the mecaseimerin clinical trials were arthralgias and myalgias; there were no adverse events of edema or carpal tunnel syndrome.

There were no reports of cancer in any of the clinical trials.

For the patients who underwent fundoscopic evaluations at baseline and during treatment there were no reports of retinopathy.<sup>34</sup>

In order to evaluate the potential risk of organomegaly associated with mecaseimerin treatment, echocardiograms, renal and splenic ultrasounds, and cephalometric X-rays (to assess specifically mandibular growth) were conducted in a subgroup of patients. Echocardiograms were done in approximately half of all patients (33/71). A few subjects (3/33) had abnormal baseline echocardiograms that normalized subsequently. Of the 30/33 patients with normal baseline echocardiograms, almost half of them (16/30) had always normal echocardiograms on treatment. Other patients had intermittently abnormal echocardiograms (9/30)<sup>35</sup> and a few (5/30) had echocardiograms that were

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<sup>33</sup> Pediatric patients treated with mecaseimerin in the diabetes development program (which included mostly type 1 and some type 2 diabetes patients) had an excess of adverse events relative to placebo for otitis media, snoring, sleep apnea, headache, hypoglycemia, hypoglycemic seizures, papilledema, and injection site hypertrophy.

<sup>34</sup> Evidence to date suggests that the increased risk of proliferative retinopathy observed with IGF-I in diabetic patients is not present in patients who do not have pre-existing retinal disease (patients with Laron Syndrome do not have retinopathy).

<sup>35</sup> They were: 1) mild pulmonary hypertension; 2) supranormal left ventricular (LV) systolic performance/left atrial dilatation; 3) large right ventricle (RV); 4) supranormal LV systolic performance, large LV and RV; 5) mild RV enlargement; 6) RV and right atrial enlargement; 7); large RV and mild cardiac chamber enlargement; 8) supranormal LV systolic performance; 9) LV and/or RV enlargement.

normal at baseline but abnormal subsequently.<sup>36</sup> The absence of a control group or standardized references for this patient population makes undisputed assignment of these findings to the study drug practically impossible. The applicant points out that none of the echocardiographic findings had clinical correlates and that there are no normative data for this patient population.<sup>37</sup>

Evaluation of abdominal organ growth (kidneys and spleen) did not substantiate the initial concern of organomegaly. The mean values and most of the individual observations were within normal limits with only occasional measurements outside the normal range.<sup>38</sup> The pattern of changes observed was that of initial “catch up” growth followed by gradual slowdown in growth acceleration, not unlike that seen for linear growth.

Although facial changes were not studied consistently during the clinical program, thickening of the nasal and lip mucosa, coarsening and overgrowth of the facial soft tissues were observed in some patients particularly at the time of puberty; reportedly, such changes appear to reverse at the discontinuation of treatment. Mandibular growth appeared to be more rapid relative to growth of the maxilla or of other skull bones; the applicant observed significant individual subject variation in facial bone growth without “clear evidence” of acromegaloid changes.

### **Clinical laboratory**

Laboratory evaluations (hematology, chemistry, thyroid function tests) were conducted in a subset of 23 patients and sporadically in other 16 patients. There were no clinically meaningful changes in mean values for up to 7 years of treatment and beyond.<sup>39</sup>

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<sup>36</sup> They included: 1) mitral valve prolapse, 2) ventricular enlargement/supranormal LV function, 3) supranormal LV systolic performance/ large LV and RV, 4) tricuspid insufficiency, and 5) small patent foramen ovale with small left to right shunt.

<sup>37</sup> Age-matched controls have much larger body sizes and height-matched controls are substantially younger. In addition, cardiomegaly is a well described feature of Laron Syndrome.

<sup>38</sup> Mean right kidney and mean left kidney SD scores at baseline were  $-3.26 \pm 1.54$ , and  $-3.01 \pm 1.71$  respectively; at last measurement they were  $-1.89 \pm 2.33$  and  $-1.69 \pm 2.47$ , respectively. Renal length SD scores exceed the upper limit of normal (i.e.,  $>2$  SD) on last measurements in only 2 subjects ( $+2.6$  and  $+2.5$ , respectively). There was no evidence of structural abnormalities.

<sup>39</sup> Some patients were followed as long as 12 years but due to the patient attrition on trial the datasets for the later years are smaller and exhibit more individual variation.

In interpreting laboratory observations outside the normal range, it is important to recognize that a variable proportion of patients had abnormal laboratory values at baseline (in some cases as many as 56%). In absence of a comparator group one cannot state with certainty whether these findings are due to the Laron Syndrome itself or to the assays used for particular evaluations. Analysis of out of range values allow for the following observations:

- There were no numerically significant or clinically relevant out of range values for hemoglobin, platelet count, total bilirubin, creatinine, BUN, total protein and albumin.<sup>40</sup> Most out of range values were either isolated or nonprogressive findings.
- Several patients had eosinophilia on trial at frequencies that were in general comparable to those observed at baseline (occasionally higher or lower).
- Lactic dehydrogenase (LDH) concentrations were high at baseline and at various times during the trial. On trial there were only four elevations  $\geq 2X$  ULN in four patients.<sup>41</sup>
- As noted above for LDH, AST levels were above normal at baseline and at different times in the trial in a significant percentage of patients; only 7 AST measurements on trial in 6 patients were  $\geq 2X$  ULN.<sup>42</sup>
- While no patient had increased ALT concentrations at baseline, several on treatment ALT elevations were observed in 6 patients during the primary IGFD clinical trials. Four of them had ALT elevations  $\geq 2 X$  ULN. Two patients (twins) had persistent elevations which peaked at 5.5 and 4.2 X ULN, respectively and subsequently normalized in one of them and remained slightly above the upper limit of normal in the other (no clear cause for these ALT elevations was identified); of the other two, one had a mild ALT elevation at the end of treatment (9-10 years) and one patient had occasional elevations while concomitantly receiving Tegretol for a seizure disorder.
- In the investigator-sponsored studies two patients had liver enzyme elevations. For one of them LFT elevations were present on re-challenge with mecasermin and a liver biopsy showed non-specific hepatocellular necrosis with neutrophilic infiltrates (“non-specific [findings] but compatible with a medication reaction”). Another patient had increased LFTs and a concomitant rash that, on skin biopsy, was “consistent to a drug reaction.”
- BUN was minimally elevated at baseline and during the trial in several patients; no elevation was  $\geq 2X$  ULN and most such elevations were followed by normal BUN values and importantly, none was accompanied by an increase in creatinine; there were no elevations in creatinine values during the clinical trial.
- There were a few occasional out of range values for serum electrolytes (calcium, phosphorus, sodium, chloride, and potassium); most were followed and/or preceded by normal values.<sup>43</sup>
- Low glucose values were observed at baseline (range of low values: 29-64 mg/dL) and on trial (range of low values: 20-64 mg/dL) in a significant proportion of patients.

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<sup>40</sup> The mean hemoglobin concentration increased substantially during the study but this is due to the fact that at baseline as many as 36.4% of patients had anemia which was corrected during the clinical trial.

<sup>41</sup> They were 3.1, 2.6, 2.9 and 2.6 X ULN, respectively.

<sup>42</sup> They were 2.1 X ULN in 3 patients, 2.0 X ULN in one patient, 2.4 X ULN in one patient and 2.2 X ULN in one patient.

<sup>43</sup> Several markedly elevated K values were observed but elevated potassium levels are notoriously unreliable in small children due to specimen hemolysis.

- Measurements of T4 and TSH levels showed occasional out of range values but no consistent abnormalities.<sup>44</sup>
- Cholesterol and triglyceride levels were elevated in a significant proportion of patients at baseline<sup>45</sup> and on trial.<sup>46</sup> The mean cholesterol and triglyceride serum concentrations appeared to increase with age and/or with treatment.<sup>47</sup> Individual cholesterol levels showed considerable variability in measurements; several subjects had marked cholesterol increases (in the 250-336 mg/dL range) or triglyceride elevations (in the 250-336 mg/dL range).
- Antibodies to IGF-I developed in 50 % of the patients evaluated (at various but not all measurements) during the first year of treatment and did not increase in titers for the second year. There were no adverse events of allergic reactions reported.

## Conclusions

Despite the absence of a control group that would allow to differentiate the adverse events associated with mecasermin treatment from the background of adverse events seen in pediatric patients in general and in patients with Laron Syndrome in particular, several conclusions can be proposed with a reasonable level of certainty; for some adverse events, however, causality is far from clear. Final conclusions (and corresponding recommendations for labeling) follow:

- Hypoglycemia in general and hypoglycemic seizures in particular can accompany mecasermin treatment. Their occurrence and severity can be reduced or mitigated by (1) careful titration of mecasermin at treatment initiation (accompanied by frequent glucose monitoring), (2) dietary advice to ensure appropriate food ingestion when mecasermin is administered, (3) availability of an emergency glucose source and/or glucagon pen, and (4) avoidance of high risk activities for older children within 2-3 hours after mecasermin injection. Consideration should be given to instructing patients at treatment initiation in a manner similar to that done for insulin.
- Lymphoid tissue hypertrophy associated with symptoms such as tonsillar enlargement, snoring, chronic middle ear effusions, sleep apnea, and need for tonsillectomy/adenoidectomy appears to occur in association with mecasermin treatment. Such adverse events can be easily monitored clinically and appropriate corrective interventions, if and when necessary, are available and common in pediatric practice.
- Adverse events similar to those described for GH treatment have been observed (e.g. arthralgia, myalgia, and papilledema). It is likely that in a larger patient population and with additional patient exposures to mecasermin additional GH-related (and IGF-I mediated)

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<sup>44</sup> One patient received thyroid replacement therapy for 3 months.

<sup>45</sup> 12/34 (35 %) of patients for cholesterol and 3/34 (11%) for triglycerides.

<sup>46</sup> Approximately 50% of the cholesterol measurements on trial were above normal as were 9 % of the triglyceride measurements.

<sup>47</sup> The mean ( $\pm$  SD) cholesterol serum concentrations increased slightly during mecasermin treatment from 170.0  $\pm$  36.5 mg/dL to 187.0  $\pm$  37.1 mg/dL. The mean ( $\pm$  SD) triglycerides increased from 78.1  $\pm$  36.6 mg/dL, to 143.7  $\pm$  103.5 mg/dL. The cholesterol-related observations are consistent with the ones reported by Laron and Klinger (Hormone Research 1993; 40 (1-3): 16-22. In this study of 13 patients with primary IGFD the mean ( $\pm$ SEM) baseline serum cholesterol level was 175.7  $\pm$  13.2 mg/dL, and increased to a mean of 191.6  $\pm$  11.3 mg/dL after 12 months of mecasermin treatment.

adverse events may be observed in the future. Therefore, it appears prudent to mention this class of adverse events in the mecasermin label.

- Injection site reactions are frequent and should be explicitly described in the label along with strategies to minimize their occurrence (injection site rotation).
- Although evidence of organomegaly has not been clearly seen, kidney and splenic lengths occasionally surpassed the 90th and the 95th percentile, respectively.
- Facial changes (coarsening and overgrowth of the facial soft tissues, thickening of the nasal lip and mucosa, faster mandibular growth relative to other facial bones), although not studied extensively, appear to occur in association with mecasermin treatment and should be mentioned in the label.
- A causal relationship between cardiac echocardiographic findings and mecasermin treatment cannot be made with certainty.
- Although there is no a priori reason to expect liver enzyme elevation in association with IGF-I (and mecasermin) replacement therapy, several patients had ALT elevations on trial; until this phenomenon is better characterized by additional clinical data, the drug label should include this information and patients should be monitored for LFT elevations.
- Clinical laboratory abnormalities in serum cholesterol, triglycerides, LDH, and AST occurred during the clinical trials; whether they are disease specific (likely) and in some patients treatment-specific, it cannot be ascertained without a control group. These findings should be labeled so that practitioners treating these patients will evaluate them in clinical practice.
- Finally, since IGF-I is an anabolic hormone very close functionally to GH, the potential risk for abuse in the marketplace needs to be acknowledged.

#### 1.3.4 Dosing Regimen and Administration

The mecasermin dosing regimen proposed in the label (80-120 µg/kg BID) is supported by data presented in this NDA and is fully consistent with data published in the medical literature (refer also to Section 8.6: Literature Review). The applicant not only has established an effective dose-regimen with respect to enhancing linear growth but has also characterized a minimally effective dose (60 µg/kg BID)<sup>48</sup> and a dose response.<sup>49</sup>

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<sup>48</sup> In this small Phase III open-label, baseline-controlled study conducted in treatment-naïve patients with growth hormone insensitivity syndrome, six patients received 60 µg/kg BID of mecasermin for one year. The mean ± SD height velocity at Month 12 was 5.4 ± 2.3 cm/yr, in excess of the baseline height velocity of 1.2 ± 0.6 cm/yr but below that observed with the to-be-marketed regimen of 80-120 µg/kg BID, which was 8.0 ± 2.2 cm. In addition, the mean change in height velocity relative to baseline for the 60 µg/kg BID regimen (4.1 cm) was inferior to the to-be-marketed regimen (5.2 ± 2.6 cm) and was not associated with significant changes in height SDS.

<sup>49</sup> Specifically, an analysis that compares the mean height velocity obtained with the 120 µg/kg BID dose versus that obtained with a ≤ 80 µg/kg BID dose indicates a statistically significant difference for Year 1 and Year 2 of treatment (p=0.0003 and p = 0.0265, respectively).

Data from the pharmacokinetic studies and on-trial IGF-I measurements following mecasermin administration indicate that the 120 µg/kg dose raises the serum IGF-I concentrations within the normal range for a few hours in patients with severe primary IGFD.

### 1.3.5 Drug-Drug Interactions

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

### 1.3.6 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, race<sup>50</sup> or co-morbid states (such as renal or hepatic failure) on mecasermin's efficacy and safety. However, several observations were made from subgroup analyses:

- There was no correlation between age and linear growth.
- Safety information accumulated during the primary IGFD clinical trials suggests that younger children may be at higher risk of hypoglycemia.
- There was no apparent gender-effect.

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<sup>50</sup> In the efficacy population 48 (79%) patients were Caucasian, 3 (5%) were African American, 6 (10%) were Hispanic, 3 (5%) were Asian, and 1 (2%) were in the "Other" category.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Mecasermin (human insulin-like growth factor-1 or rhIGF-I, proposed commercial name: Increlex) is a synthetic version of the 70 amino acid, single chain, native IGF-I protein.<sup>51</sup> Mecasermin is synthesized in an E.coli vector by recombinant DNA technology, subsequently purified and finally formulated as a 10 mg/ml sterile solution in a 5 ml vial for subcutaneous injection. Mecasermin is a new molecular entity.

IGF-I is a hormone structurally related to insulin. Under physiological conditions IGF-I is the main mediator for the actions of growth hormone (GH) at the growth plate, actions that are ultimately responsible for linear (statural) growth. Deficiencies in GH and IGF-I production result in severe short stature. Most patients with short stature are treated successfully with GH, an approved drug product that has been used in children and adults for approximately 4 decades. A subset of patients with short stature has mutations at and beyond the level of the GH receptor (GHR) and does not respond to GH.<sup>52</sup> For these patients IGF-I bypasses the GHR molecular defect.

The proposed indication for mecasermin is “long-term treatment of growth failure in children with primary IGF-I deficiency”<sup>53</sup> and children with GH gene deletion.<sup>54</sup> The

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<sup>51</sup> Mecasermin is not glycosylated and contains three intramolecular disulfide bridges (molecular weight =7649 daltons).

<sup>52</sup> Several clinical terms have been used to describe these patients: growth hormone resistance, GH insensitivity syndrome (GHIS) primary IGF deficiency (primary IGFD). Within these syndromes some conditions are well characterized such as GHR mutations (Laron Syndrome), postreceptor defects, IGF-I gene deletions.

<sup>53</sup> This is further and specifically characterized by (1) a height standard deviation score that is less than or equal to -3.0, (2) a basal IGF-1 standard deviation score less than or equal to -3.0, and (3) normal or elevated growth hormone level.

<sup>54</sup> Patients with GH gene deletion respond initially to GH but subsequently developed neutralizing antibodies to exogenously administered GH, which render GH treatment ineffective.

target population is estimated between 350 patients (Laron Syndrome) and several thousands for the “extended” indication. Primary IGFD is an orphan disease.

Mecasermin is a new molecular entity. Due to its potential hypoglycemic effect it is to be administered with meals. It is given as a subcutaneous injection twice a day at a dose of 80-120 µg/kg. As is the case with GH, mecasermin treatment is to be initiated in early childhood and continued up to the point of epiphysial closure.

## **2.2 Currently Available Treatment for the Indication**

Currently there are no approved treatments for the primary IGFD indication in the US.<sup>55</sup>

## **2.3 Availability of Proposed Active Ingredient in the United States**

Mecasermin has not been approved in the US for other indications.

## **2.4 Important Issues With Pharmacologically Related Products**

The action of IGF-I is intimately connected with that of growth hormone (approximately 80% of the GH effect on growth is IGF-I mediated).<sup>56</sup> There is wide clinical experience with GH in both children and adults: in the last half-century over 200,000 patients have been treated with GH. Adverse events (AEs) described with GH are: pseudotumor cerebri, joint pain, myalgia, edema, unmasking of underlying hypothyroidism, slipped capital femoral epiphyses during rapid growth, gynecomastia, insulin resistance. Although it is not known to what extent the GH adverse event

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<sup>55</sup> Other rhIGF-1 preparations have been approved for use in Europe and Japan. The applicant states that “in 1994, mecasermin (Pharmacia, now Pfizer) was approved for the treatment of growth hormone insensitivity in pediatric 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 pediatric patients. The product is still marketed in Japan. We know of no unexpected postmarketing safety issues associated with the Fujisawa product.”

<sup>56</sup> Specifically, a GH molecule binds two cell-surface GH receptors (or, alternatively, it binds to a preformed GH receptor dimer) primarily in liver but also in many other tissues. This binding triggers a series of sequential intracellular events such as intra-cellular phosphorylation of the GH receptor, activation of intracellular GH signal transduction protein pathways (including MAP Kinase, JAK2 and STAT5). Such signals activate the IGF-1 gene, resulting in IGF-1 synthesis and secretion, and increased blood IGF-1 levels.

profile will overlap with that of IGF-I, it is expected that some of the GH-associated AEs will be encountered with IGF-I treatment.

IGF-1 is structurally related to insulin, binds the insulin receptor (albeit with a lower affinity than the IGF-I receptor) and consequently has “insulin-like” metabolic activities, including the risk of inducing hypoglycemia.

## **2.5 Presubmission Regulatory Activity**

An End-of-Phase-2/General Guidance Meeting<sup>57</sup> and a pre-NDA meeting<sup>58</sup> took place between the Division and the applicant. In both meetings the division has provided general guidance to the applicant (for specifics see Meeting Minutes in DFS).

## **2.6 Other Relevant Background Information**

The Japanese label<sup>59</sup> for mecasermin (Somazon®) lists the following adverse events: hypoglycemia, hypersensitivity reactions, organ growth,<sup>60</sup> deterioration of hypertrophic cardiomyopathy, polycystic ovary, injection site reactions, edema, worsening in diabetic retinopathy. Malignancy is the only contraindication to treatment listed in the label. The dose approved for the growth hormone insensitivity syndrome indication is 50-200 µg/kg once to twice a day.

# **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

## **3.1 CMC (and Product Microbiology, if Applicable)**

The final CMC review is pending at this time. A partial review in DFS recommends a decision of “Approvable” pending additional CMC information requested from the applicant (and soon to be submitted) and a satisfactory cGMP inspection.

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<sup>57</sup> March 5, 2003.

<sup>58</sup> May 27, 2004.

<sup>59</sup> Internally translated.

<sup>60</sup> Listed organs are pituitary, tonsils, submandibular glands, spleen, kidney, and ovary.

### **3.2 Animal Pharmacology/Toxicology**

The pharmacology/toxicology review has been completed and recommends that mecasermin should be approved. Labeling recommendations have been incorporated in the line-by-line-labeling review (see Appendix).

### **3.3 Statistical Review**

The final statistical review is pending. Preliminary discussions with the statistical reviewer did not identify any approvability issues to date.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The source of efficacy and safety clinical information in this review is the five clinical trials of mecasermin conducted in children with primary IGFD (see next section for a table summary these studies). The structure of the primary IGFD clinical program is detailed in Section 6.1.3. Several rhIGF-I clinical trials conducted in patients with primary IGFD published to date are summarized by this reviewer in Section 8.6. Where relevant, clinical safety data from the mecasermin Type 1 and Type 2 diabetes program is mentioned.

### **4.2 Tables of Clinical Studies**

The main characteristics of the five clinical studies of mecasermin conducted in patients with primary IGFD are summarized in applicant's Table 9.1-1. All but one of these studies were baseline-controlled, open-labeled clinical trials (Study F0375 was the only double-blind, placebo-controlled mecasermin trial, albeit a small one). Patients enrolled in the early clinical studies (F0206s, F0375g, F0632g) were subsequently rolled into Study F0671g, which later became the investigator-sponsored Study 1409 (F0930s).

Table 9.1-1: Safety and Efficacy Studies

Study	IND #	Phase	Number of Subjects	Duration	Doses Used	Process/Formulation	Study Design
F0206s	—	2	8	2 years	80-120 µg/kg BID	— citrate	Open-label, Investigator sponsored
F0375g	39,679	3	8	2 years	80-120 µg/kg BID	— citrate	Double-blind placebo controlled, crossover
F0632g	39,679	3	6	1 year	60 µg/kg BID	— /citrate	Open-label
F0671g	39,679	3	23	2 years	80-120 µg/kg BID	— /acetate	Open-label Multi-center
1419 (F0930s)	—	3	70*	Ongoing since 1998	80-120 µg/kg BID	— /acetate	Open-label, Multi-center Investigator sponsored

\* as of December 2003

### 4.3 Review Strategy

Clinical trial 1419 was reviewed in detail because it includes all the clinical trials included in the mecasermin clinical program in primary IGFD (patients from all previous clinical trials were “rolled” into Study 1419). The efficacy analysis of this clinical trial is in essence an integrated summary of efficacy. Similarly, the safety dataset of trial 1419 includes the datasets of all the individual studies and acts as an integrated summary of safety. Independent safety analyses from SAS transport files were also conducted and described in the appropriate sections, as is the 120-day safety update.

### 4.4 Data Quality and Integrity

There was no DSI audit. This reviewer did not identify any significant inconsistencies between various datasets and text/figures in the analyses completed.

### 4.5 Compliance with Good Clinical Practices

The applicant states that “study [1419] was conducted in accordance with the ethical and regulatory guidelines in place at the beginning of the study and updated as appropriate

and any national and international requirements.” The protocols and informed consent documents were, reportedly, approved by the institutional review boards at the participating sites.

#### 4.6 Financial Disclosures

Two clinical investigators conducted most of the clinical studies submitted with this NDA: Dr. Louis Underwood (University of North Carolina) and Dr. Steven Chernausek (Children’s Hospital Medical Center, Cincinnati). According to Form 3455 submitted on his behalf, Dr. Underwood

It is important to mention that Dr. Underwood continued to treat patients with primary IGF-I in Study 1419 after Genentech discontinued the IGF-I development program. According to Form 3455 submitted on his behalf, Dr. Steven Chernausek

Dr. Chernausek

The applicant completed Form FDA 3454 on behalf of five other clinical investigators which states that they

“did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).”

The clinical information accumulated in Study 1419 after 1998 was generated in large part by several endocrinologists at different sites around the world. Each of these sites enrolled a small number of patients.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The physiologic functions of IGF-I have been extensively characterized and a large body of publications is available on this topic.<sup>61</sup> The applicant presents information on the

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<sup>61</sup> The tissue availability of IGF-I is determined by six IGF binding proteins (IGFBP-1 through 6). Under normal circumstances over 95 % of circulating IGF-I is protein bound, with > 80% being part of a multimolecular complex

**Table 2.5.3.2-1: Mean Total IGF-1 Pharmacokinetic Parameters after SC Administration of Mecasermin in Subjects with Severe IGFD**

Clinical Rev {Dragos Ror {21-839/N 0 {Increlex (m	Single Dose (MS302)				Multiple Dose Simulation		
	Dose (mg/kg)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	AUC(0-∞) (µg·min/mL)	t <sub>1/2</sub> (hr)	C <sub>max</sub> (µg/mL)	AUC <sub>0-12hr</sub> (µg·min/mL)
	0.015	0.059	2.67	43.0	9.4	0.0833	439
	0.030	0.116	2.67	56.6	3.9	0.149	623
	0.060	0.170	3.33	125	9.7	0.217	980
	0.120	0.234	2.00	176	5.8	0.375	1659

Single dose data from study MS302 were analyzed using noncompartmental methods  
 N=12, 3 subjects per dose level, aged 12 to 22 yr  
 Male and female data combined, 3 male, 9 female  
 The single dose data in study MS302 and population PK model parameters developed from the single dose data were used to simulate the multiple dose data.  
 Data in study MS302 were corrected for endogenous total IGF-1 concentrations; data in the multiple dose simulation were not corrected for endogenous total IGF-1 concentrations  
 Source: MS302, Multiple Dose Simulation Report

pharmacokinetics of mecasermin for several doses including the to-be-marketed dose of 120 µg/kg. The applicant proposes the following observations:

- the mean total IGF-1 C<sub>max</sub> and AUC values increased with increasing doses (less than dose proportionally)
- T<sub>max</sub> and t<sub>1/2</sub> did not change substantially with increasing single doses
- the 120 µg/kg mg/kg dose raised total IGF-1 concentrations into the normal range for a few hours (no subjects in this cohort had a similar response at lower doses)<sup>62</sup>

During the clinical trial 1419, IGF-I serum concentrations were measured pre-dose and two hours post-dose at various timepoints. Pre-dose measurements were done in 34 subjects for a total of 134 measurements. Post-dose measurements were done in 26 subjects for a total of 122 measurements. The results are summarized in Table 1. Pre-dose, the mean IGF-I serum levels were extremely low (SD score of -3.6 ± 3.0). On treatment they reached levels in the normal range (-1.8 ± 2.14). The on-treatment IFG-I serum levels were, as expected, higher for the 120 µg/kg dose relative to the 80 µg/kg dose (SD scores: -2.1 ± 2.6 vs. -1.7 ± 2.0).

**Table 1: IGF-I Pharmacokinetics\***

Statistics	Pre-dose (No. of patients = 34)	Post-dose (No. of patients = 26)
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with IGFBP-3 and the acid labile subunit. The IGFBPs (in particular IGFBP-3) limit the distribution and elimination of IGF-I (i.e. free IGF-1 is cleared at a faster rate than IGF bound to IGFBPs). Endogenous IGF-1 and IGFBP-3 are greatly reduced in subjects with Primary IGFD, resulting in differences in IGF-1 PK characteristics relative to normal subjects..

<sup>62</sup> In subjects with moderate IGFD (who do not represent the patient population studied in this NDA), all subjects experienced a rise in total IGF-1 concentrations to within or above the normal range with doses of 0.03 mg/kg or higher.

<b>IGF-1 (ng/ml)</b>		
No. of measurements	164	122
(mean ± SD)	51.7 (57.79)	119.7 (112.92)
range	[-	] -
<b>IGF-1 SD Score</b>		
No. of measurements	164	122
(mean ± SD)	-3.6 (2.98)	-1.8 (2.14)
range	[-	] -

\* serum concentrations

Source: Table 16.2.10 in Section 5.3.5.2.4.

## 5.2 Pharmacodynamics

The applicant states that “no PK/PD studies were designed specifically to relate growth in children with severe IGFD to IGF-1 concentrations after administration of mecasermin.” Pharmacodynamic parameters such as GH, glucose, and IGFBP-3 were measured in several studies. Several observations such as down-regulation of GH in the presence of normalization of serum IGF-I levels or the hypoglycemic effect of IGF-I are already well documented.<sup>63</sup> In one study (Study F0317g) mecasermin had no effect on appetite.

## 5.3 Exposure-Response Relationships

There were no formal exposure-response assessment performed. Most of the dosing information comes from dose-response observations.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

<sup>63</sup> The acute hypoglycemic effect of rhIGF-1 is similar in time course to that of insulin and can be blunted or blocked by taking a meal at the time of dosing.

The proposed indication (as stated in the Indications and Usage section of the applicant's proposed label) is as follows:

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#### 6.1.1 Methods

Refer to Sections 4.1 and 4.3.

#### 6.1.2 General Discussion of Endpoints

The primary and secondary endpoints of the mecasermin clinical trials are standard endpoints evaluated in pediatric statural studies. The applicant's choice of endpoints is in agreement with prior recommendations made by the division.

#### 6.1.3 Study Design

As further described in this section, Study 1419 integrates all the mecasermin clinical studies conducted in patients with primary IGFD and is described next.

#### **Objective**

The stated objective of the study was to “evaluate the safety and efficacy of mecasermin administered SC [subcutaneously] BID [twice daily] in children with growth failure due to Primary IGFD.”

## Design

Study 1419 is an investigator-sponsored, open-label clinical trial of mecasermin conducted in patients with primary IGFD. This study, conducted under IND ~~1419~~,<sup>64</sup> includes to date 70 patients; of these, 41 patients (59%) were naïve to treatment and 29 patients (41%) were treatment-experienced. The vast majority of the treatment-experienced patients were initially enrolled in several small studies of mecasermin and were subsequently transferred to study 1419. The studies that proceeded study 1419 are listed below:

- Study F0206s was an open-label, baseline-controlled, 2-year study that included 8 subjects who received 80-120 µg/kg of mecasermin BID.<sup>65</sup>
- Study F0375g was a placebo-controlled, crossover study of mecasermin or placebo treatment for 6 months, followed by a 3-month washout period, a 6-month crossover period and, finally, a 12-month open-label extension phase (the mecasermin dose was 80-120 µg/kg given BID).<sup>66</sup> It was conducted in 8 patients.
- Study F0632g was a 1-year, open-label, baseline-controlled study designed to evaluate low dose mecasermin therapy (60 µg/kg, BID); it enrolled six treatment-naïve subjects. (including one patient who had been previously enrolled in Study F0375g in the placebo group).<sup>67</sup>

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<sup>64</sup> IND owner: ~~L~~ 1 Initiation of the study dates back to May 20, 1991. The study is ongoing. The date of the study report is December 3, 2004.

<sup>65</sup> This Phase 2 study was conducted under IND ~~C~~ 1 it was initiated on May 20, 1991 and was completed on December 5, 1995.

<sup>66</sup> This Phase 3 study was conducted under IND 39,679; it was initiated on August 3, 1992 and was completed on March 12, 1996.

<sup>67</sup> This Phase 3 study was conducted under IND 39,679; it was initiated in July 1994 and completed in February 1996.

- Study F0671g was an open-label, multi-center trial of mecasermin. It included twenty-three subjects: 21 were from the above-mentioned studies (F0206s, F0375g, and F0632g) and 2 patients were treatment-naive.<sup>68</sup> The study was initially part of Genentech's IGF-I development program but was terminated when Genentech decided to stop the IGF-I program in diabetes.<sup>69</sup> After study closure, subjects were 'rolled' in the investigator-sponsored open-label Study 1419. Patients were treated with mecasermin doses of 80-120 µg/kg given BID.

The applicant states that the patients who were transferred to study 1419 have received mecasermin treatment uninterruptedly. A graphic description of trial design and subject enrollment is presented in applicant's Figure 9.1-1. With the exception of study F0375g a (randomized placebo-controlled, crossover study) all other studies had no control group (they were baseline-controlled for efficacy analyses). The patient population consisted in subjects with either GH receptor defects (Laron Syndrome) or subjects with GH gene-deletion defects who developed anti-GH neutralizing antibodies.

During the mecaasermin program, patients were initially titrated in an in-patient setting to a well tolerated dose (i.e. a dose that was not associated with hypoglycemia) and only subsequently discharged home on a specific IGF-I dose regimen.<sup>70</sup> Occasionally, down-

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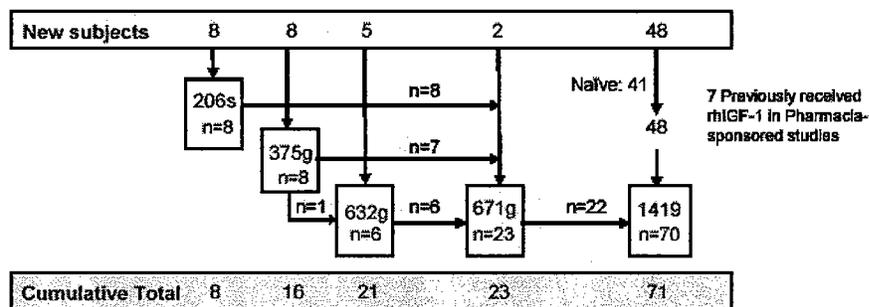
<sup>68</sup> This Phase 3 study was conducted under IND 39,679; it was initiated on November 6, 1995 and was completed on June 29, 1998.

<sup>69</sup> Tercica acquired the intellectual rights for the rhIGF-I Genentech program in 2002.

<sup>70</sup> In Study F0206s, conducted [ study at University of North Carolina (UNC), subjects were admitted to the General Clinical Research Center for 19 days. Mecasermin was titrated from 40 µg/kg SC as BID injections to 120 µg/kg SC BID. The injections were administered immediately before breakfast and prior to a late afternoon snack. Subjects were discharged home on a dose of 120 µg/kg SC BID and instructed on home blood glucose monitoring and how to treat hypoglycemia. The subjects returned monthly for follow-up during the first year of therapy, bimonthly during the second year of therapy, every 3 months during Years 3 and 4, and every 6 to 12 months thereafter. Visits alternated between UNC and the referring pediatric endocrinologists. Studies F0375g and F0632g were both conducted at the Children's Hospital Medical Center Cincinnati (CHMCC) by Dr. Steven Chernausk. Subjects were hospitalized for 5 days during which time the mecasermin dose was titrated up to 120 µg/kg SC BID (Study F0375g) and up to 60 µg/kg SC BID (Study F0632g). After discharge subjects were follow-up at CHMCC every 3 months. During the long-term follow-up Study F0671g the frequency of visits was reduced to every 6 months at UNC and CHMCC. In Study 1419 subjects previously treated in Study F0671g have been seen at least annually at either UNC or CHMCC. New subjects enrolled since 1998 by pediatric endocrinologists internationally have been seen for dose titration and follow-up by their referring pediatric endocrinologist in consultation with Dr. Underwood. Progress reports including interval height, weight, and reports of any adverse

titration of the dose was necessary. Mecasermin was administered SC in the morning and in the evening before a meal at doses ranging from 60 µg/kg to 120 µg/kg BID).<sup>71</sup>

Figure 9.1-1: Subject Enrollment \*



\*Subject enrollment as of December 2003

### Inclusion/exclusion criteria

The main criteria for enrollment across the 5 studies were consistent with a diagnosis of primary IGFD. They included: short stature, low IGF-I SD score, GH sufficiency, and (for patients with GH deletion) evidence of neutralizing antibodies. The specific requirements of these inclusion criteria are listed below:

- height standard deviation score < -2
- height velocity < 50th percentile for age and sex
- IGF-I standard deviation score < -2
- age > 2 years
- failure to increase IGF-1 by 50 ng/mL in response to exogenous recombinant human GH at a dose of 0.1 mg/kg/day

event were reviewed by Dr. Underwood prior to providing additional mecasermin. (As naïve subjects enrolled in Study 1419 after 1998 had the dose titration and follow-up visits performed by local referring pediatric endocrinologists throughout the world, laboratory assessments and special study procedures were generally not available for these patients).

<sup>71</sup> The 60 µg/kg BID regimen was administered in only one study (Study F0632). All other studies employed an 80-120 µg/kg BID regimen.

- random or stimulated growth hormone concentration  $\geq 10$  ng/mL (except for subjects with GH gene deletions who had to have anti-GH antibodies with a binding capacity  $>10$   $\mu$ g/mL)

Patients were not allowed study participation if they had (1) active malignancy or any history of malignancy, (2) growth failure due to other etiologies such as endocrine, chronic, or genetic conditions, (3) prior treatment with corticosteroids or other medications that influence growth, and (4) clinically significant electrocardiogram abnormalities or a history of clinically significant cardiac arrhythmia.

#### Treatment compliance

The applicant states that “in Study 1419, compliance with injection regimen was assessed by the local referring pediatric endocrinologists.” In previous studies (F0206s, F0375g, F0632g, and F0671g) compliance was evaluated by recording in a calendar the number of injections given and by keeping track of the number of used and unused vials.

#### Prior and Concomitant Therapy

Eight subjects received rhIGF-I prior to enrollment (mainly in study 1419; they participated in Pharmacia’s IGF-I development program). One of them received rhIGF-I only for 2 weeks and was assigned to the treatment-naive group for efficacy analysis. The efficacy for the other 7 subjects is discussed individually in the NDA. Eleven patients received Lupron® in order to delay puberty (the applicant states that “no special adjustments have been made for the efficacy analysis in this subgroup”).

## Drug Concentration and Anti-IGF-I Antibody Measurements

Measurements of study drug (i.e. IGF-I) concentrations were done in 3 studies (F0375g, F0632g, and F0671g). They included trough and 2-hour post dose measurements for serum or plasma IGF-1 and were completed during the initial in-hospital dose titration phase and subsequently at 3 to 6-month intervals.<sup>72</sup>

Anti- IGF-1 antibodies were measured using an ELISA assay.<sup>73</sup>

## Protocol amendments

Studies F0206s and Study F0375g were amended to include the 80 µg/kg BID dose regimen.

## Subject disposition

Subject disposition and reasons for study discontinuation across all mecasermin studies are presented in applicant's Table 10.1-1. The mecasermin clinical program includes a total of 71 subjects. Of the patients enrolled in the Genentech studies, all but one continued in Study 1419.<sup>74</sup> Eleven (15.5%) subjects discontinued mecasermin treatment: 4 were non-compliant, 5 were lost for follow-up, one exhibited poor growth,

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<sup>72</sup> IGF-I serum/plasma concentrations were measured using Genentech's in-house IGF-1 radioimmunoassay.

<sup>73</sup> The negative and positive controls were "pooled normal volunteer sera and human sera spiked with rabbit antihuman IGF-I antibodies, respectively." Results are reported as the base-10 logarithm of the dilution giving greater optical density than the negative control; e.g., a titer of 2 indicates that the specimen was positive in a 1:100 dilution

<sup>74</sup> Study 1419 included a total of 70 subjects: 22 subjects from the Genentech studies, 7 patients previously treated in the Pharmacia IGF-I studies, and 41 treatment-naïve patients.

and one discontinued because of parent-subject decision. Currently, 53 (74.6%) patients are still continuing the treatment.

**Table 10.1-1: Disposition of Subjects (n=71)**

	<b>Total</b>
<b>Subjects Enrolled</b>	71
<b>Status</b>	
Completed F0671g, did not enroll in 1419	1 (1.4%)
Attained near-adult height	6 (8.5%)
Ongoing	53 (74.6%)
Early Discontinuation	11 (15.5%)
<b>Primary Reason for Early Discontinuation</b>	
Non-compliance	4 (5.6%)
Parent/Subject Decision	1 (1.4%)
Lost to Follow-up	5 (7.0%)
Poor Growth	1 (1.4%)

## Protocol Deviations

The applicant reports that 58/71 subjects fully satisfied the inclusion criteria. Several “enrollment deviations” were reported (4 in previously treated subjects and 9 in treatment-naïve subjects) and are summarized next:

- four subjects were previously treated with Pharmacia’s rhIGF-I and were subsequently enrolled in Study 1419; although these subjects were believed to have primary IGFD in the judgement of the investigators, formal documentation was missing; none of these subjects was, however, included in the efficacy analysis since none had one year of data at the time of datalock.
- one subject (18-011) had a GH receptor abnormality proven by genetic sequencing, and was enrolled via waiver despite no documentation for an elevated GH level.
- six subjects (10-920, 10-922, 10-931, 10-937, 18-005, 18-006) had a phenotype consistent with Primary IGFD (including extreme short stature (height SD score  $\leq$  -6.5) and GH levels of  $> 10$  ng/mL). All 6 of these subjects were permitted enrollment despite absent IGF-1 levels or IGF-1 SD scores  $> -2$ .

- one subject (10-925) was classified as having GH gene deletion but documentation of the anti-GH antibody status was lacking).
- in one subject (10-915) GH deficiency could not be ruled out biochemically because no basal evaluation of the GH status was documented; this patient had height SD score of -4.9 and was IGF-1 deficient (IGF-1 SD score of -9.5), According to the applicant, “this is the only subject in whom Primary IGFD could not be confidently predicted on the basis of the available information.”

### Demographics and baseline patient characteristics

The patient characteristics at baseline for all subjects enrolled and for subjects who contributed data to the primary analysis (one-year evaluable population) are presented in Table 2. The baseline characteristics for the two patient populations are comparable.

The patients included in the one-year evaluable population were characterized by extreme short stature (mean height SDS of -6.7; range: -12.1 to -2.8), low serum IGF-I concentrations (mean: -4.3; range: -9.5 to -0.7), and very poor growth rates (mean height velocity: 2.8 cm/yr). The vast majority of patients (56 or 92%) were prepubertal. Thirty seven (61%) of the subjects were male and 24 (39%) were female. Most patients were Caucasian (48 patients or 79%), followed by Hispanics (6 patients or 10%), African American and Asian (3 patients or 5% each), and “Other” (1 patient or 2%). Patients were enrolled from 19 different countries throughout the world. Most patients were from Saudi Arabia (16 patients or 26%), followed by USA (12 or 26 %), Argentina (6 or 10%), Italy (5 or 8 %), Iran and Taiwan (3 or 5 %, each), Egypt, Kuwait and Russia (each contributing 2 patients or 3%); all other countries contributed only one patient (2%) each. Fifty-six (92%) were reported or imputed to be prepubertal (Tanner stage I); only one patient (2%) was Tanner Stage II at baseline; four patients (6 %) had Tanner

stage unknown (undocumented) at baseline. Fifty-three (87 %) of all patients had Laron Syndrome phenotype; 7 (11%) had GH gene deletion<sup>75</sup> and 1 (2% had GH antibodies).

**Table 2: Baseline Characteristics for All Enrolled Subjects (n=71) and for Subjects Who Completed At Least One Year of Treatment (n=61)**

Variable	All subjects			One-year*		
	N	Mean ± SD	Range	N	Mean ± SD	Range
Age (years)	71	7.6 ± 4.4	1.7 to 17.5	61	6.7 ± 3.8	1.7 to 15.2
Height (cm)	69	89.5 ± 20.5	61.3 to 151.4	61	84.8 ± 15.3	61.3 to 133.1
Height SDS	69	-6.5 ± 1.9	-12.1 to -2.8	61	-6.7 ± 1.8	-12.1 to -2.8
HV (cm/yr)	66	2.9 ± 1.9	0.0 to 7.7	58	2.8 ± 1.8	0.0 to 7.7
HV SDS	64	-3.1 ± 1.8	-6.6 to 1.8	58	-3.3 ± 1.7	-6.6 to 0.9
IGF-1 (ng/mL)	64	21.2 ± 20.3	0.2 to 82.1	56	21.6 ± 20.6	0.2 to 82.1
IGF-1 SDS	64	-4.4 ± 1.7	-9.5 to -0.7	56	-4.3 ± 1.6	-9.5 to -0.7
Weight (kg)	66	14.4 ± 8.7	5.8 to 42.5	59	12.5 ± 6.0	5.8 to 35.0
BMI (kg/m <sup>2</sup> )	64	16.8 ± 2.9	12.8 to 26.4	59	16.5 ± 2.5	12.8 to 24.6
BMI SDS	62	-0.1 ± 1.2	-3.1 to 2.2	57	-0.2 ± 1.2	-3.1 to 2.2
Bone Age (yrs)	66	4.9 ± 3.5	0.3 to 14.0	57	4.2 ± 2.8	0.3 to 12.3
Max. GH (ng/mL)*	62	54.4 ± 45.5	0.5 to 209.0	55	55.7 ± 46.2	0.5 to 209.0

\*Subjects with at least one year of treatment (evaluatable population).

\*\* Maximum Growth Hormone concentration.

N= number of patients counted; HV = pre-treatment height velocity. IGF-I = baseline IGF-I.

Source: Tables 11.1-2 and 16.2.4.2 (Section 5.3.5.2.4).

## 6.1.4 Efficacy Findings

### Primary Efficacy Analysis

#### Height velocity

<sup>75</sup> Three of the 7 subjects with GH gene deletion were reported as having had anti-GH antibodies.

Sixty-one of the 71 subjects enrolled in enrolled in the clinical program completed at least one year of mecasermin treatment; of these, 58 subjects had both baseline and post-treatment height velocities and were thus included in the primary efficacy analysis.

On mecasermin treatment, the mean height velocity increased from  $2.8 \pm 1.8$  cm/yr (range 0.0 to 7.7 cm) at baseline to  $8.0 \pm 2.2$  cm/yr (range 1.8 to 12.8 cm at the end of Year 1 (Table 3). This finding was statistically significant (paired t-test p-value < 0.0001). The mean height velocities for Year 2 through Year 6 were all statistically higher than baseline HV (the mean height velocities observed for Year 2 through Year 6 were  $5.8 \pm 1.5$  cm/yr (Year 2),  $5.5 \pm 1.8$  cm/yr (Year 3),  $4.7 \pm 1.6$  cm/yr (Year 4),  $4.7 \pm 1.5$  cm/yr (Year 5), and  $4.8 \pm 1.5$  cm/yr (Year 6), respectively). Height velocity change for Year 7 indicated a trend toward statistical significance but the height velocity for Year 7 was not statistically significant. It is important to note that the number of subjects contributing data at Years 7 and 8 were only 16 and 13, respectively. The applicant does not report any statistically significant differences in Year 1 height velocity between males (n=37) and females (n=24)<sup>76</sup> or between subjects with growth hormone gene deletion (n=7) and subjects with Laron Syndrome phenotype (n=53).<sup>77</sup> The yearly changes ( $\pm$  SD) change in HV relative to baseline were:  $5.2 (\pm 2.6)$ ,  $2.9 (\pm 2.4)$ ,  $2.3 (\pm 2.4)$ ,  $1.5 (\pm 2.2)$ ,  $1.5 (\pm 1.8)$ ,  $1.5 (\pm 1.7)$ ,  $1.0 (\pm 2.1)$ , and  $0.7 (\pm 2.5)$  cm/yr. for Years 1 through 8, respectively.

Table 3: Annual Height Velocities by Number of Years treated with Mecasermin

Statistics	Year 1 (N=58)	Year 2 (N=48)	Year 3 (N=38)	Year 4 (N=23)	Year 5 (N=21)	Year 6 (N=20)	Year 7 (N=16)	Year 8 (N=13)
Mean (SD)	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)
Median	8.3	5.8	5.5	5.0	4.9	4.6	4.1	4.5

<sup>76</sup> p=0.39 (t-test).

<sup>77</sup> p= 0.61 (t-test).

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<b>Range</b>	1.8, 12.8	1.5, 8.9	2.2, 10.8	2.0, 7.7	2.1, 8.3	2.7, 8.5	2.4, 7.2	2.6, 5.8
<b>Change*</b>	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)
<b>p-value**</b>	<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
<b>95 % CI***</b>	4.5, 5.9	2.2, 3.6	1.6, 3.1	0.5, 2.4	0.6, 2.3	0.7, 2.3	-0.2, 2.1	-0.8, 2.3

\*Mean (SD) for change from pre-dose.

\*\* Paired t-test for change from pre-dose.

\*\*\* CI = confidence interval for change from pre-dose

Source: Table 11.3.1-1 in 5.3.5.2.4 Study report 1419.

At the request of the Division, the applicant conducted a subgroup efficacy analysis restricted to the treatment-naïve patients enrolled in study 1419 (i.e. excluding data obtained from patients initially evaluated in other studies and subsequently “rolled” into Study 1419). The results of such an analysis for HV (cm/yr) are presented in Table 11.3.1-2 for three years of treatment. The results are consistent with those of the primary analysis. Specifically, in 15 subjects who contributed data for 3 years, mean height velocities at Year 1, 2, and 3 were 8.9, 5.9 and 6.4 cm/yr, respectively; these findings were statistically significant ( $p \leq 0.0001$ ).

**Table 11.3.1-2: Annual Height Velocity (Subjects in Study 1419 Naïve to Mecasermin)**

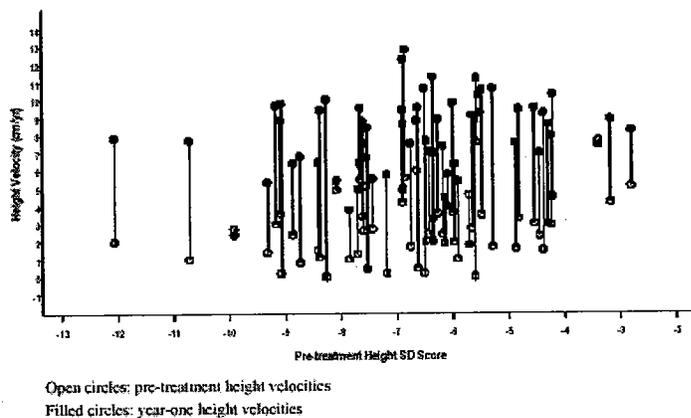
	Pre-dose	Year 1	Year 2	Year 3
<b>Subjects Completing ≥1 Year</b>				
N	35	35		
Mean (SD)	2.5 (1.7)	8.3 (1.9)		
Median	2.4	8.6		
Min, Max	0.0, 7.6	1.8, 12.3		
Mean (SD) for change from pre-dose	N/A	5.8 (2.5)		
P-value for change from pre-dose [1]	N/A	<0.0001		
95% CI for change from pre-dose	N/A	(5.0, 6.7)		
<b>Subjects Completing ≥2 Years</b>				
N	25	25	25	
Mean (SD)	2.6 (1.8)	8.8 (1.7)	5.8 (1.7)	
Median	2.4	8.9	5.9	
Min, Max	0.0, 7.6	4.9, 12.3	1.5, 8.9	
Mean (SD) for change from pre-dose	N/A	6.2 (2.2)	3.3 (2.2)	
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	
95% CI for change from pre-dose	N/A	(5.3, 7.1)	(2.4, 4.2)	
<b>Subjects Completing ≥3 Years</b>				
N	15	15	15	15
Mean (SD)	3.0 (1.9)	8.8 (2.0)	5.9 (1.3)	6.2 (2.2)
Median	3.3	8.9	5.9	6.4
Min, Max	0.0, 7.6	4.9, 12.3	2.7, 8.4	2.5, 10.8
Mean (SD) for change from pre-dose	N/A	5.8 (2.2)	2.9 (1.8)	3.3 (2.4)
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	0.0001
95% CI for change from pre-dose	N/A	(4.6, 7.1)	(1.9, 3.9)	(1.9, 4.6)

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

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Individual height velocity data are presented in applicant's Figure 11.3.1-1; measurements before treatment are displayed as open circles and those during the first year of treatment as closed circles; the measurements are displayed horizontally in ascending order of pre-treatment height SD scores. The vast majority of individual responses indicated an increase in height velocity on treatment. This observation applied across a wide range of baseline height SD scores.

Figure 11.3.1-1: Pre-treatment Height Velocity and First Year height Velocity Versus Pre-treatment Height SD Score Subjects Naïve to Mecasermin



### Height velocity SDS

An analysis of mean height velocity SDS yielded results similar to those reviewed in the previous paragraphs (Table 4). The mean height velocity SD score at baseline was -3.3. It increased to 1.9 after one year of treatment; this increase was statistically significant ( $p < 0.0001$ ). The mean height velocity SD score remained elevated relative to that recorded at baseline for Years 2 through 8 (-0.2, -0.2, -0.7, -0.6, -0.4, -0.4, and -0.4, respectively; all values were statistically greater than baseline HVSDS).

Table 4: Annual Height Velocity SDS by Number of Years treated with Mecasermin

Statistics	Year 1 (N=58)	Year 2 (N=47)	Year 3 (N=37)	Year 4 (N=22)	Year 5 (N=19)	Year 6 (N=18)	Year 7 (N=15)	Year 8 (N=11)
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Mean (SD)	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)	-0.4(1.9)
Median	1.7	- 0.3	-0.4	-1.0	-0.6	-0.6	-0.1	-0.4
Range	-4.4, 15.4	-4.8, 3.2	-4.1, 5.5	-4.4, 3.9	-3.8, 5.3	-3.1, 2.0	-3.9, 3.2	-2.7, 4.3
Change*	5.2 (3.1)	3.1 (2.3)	2.9 (2.3)	2.2 (2.2)	2.5 (2.2)	2.7 (1.7)	2.5 (2.1)	2.7 (2.8)
p-value**	<0.0001	<0.0001	<0.0001	0.0001	0.0001	<0.0001	0.0003	0.0086
95 % CI***	4.4, 6.0	2.5, 3.8	2.1, 3.7	1.2, 3.1	1.4, 3.6	1.9, 3.5	1.4, 3.7	0.9, 4.6

\*Mean (SD) for change from pre-dose.

\*\* Paired t-test for change from pre-dose.

\*\*\* CI = confidence interval for change from pre-dose

Source: Table 11.3.2-1 in 5.3.5.2.4 Study report 1419.

Comparable observations were made when the same analysis of HVSDS was applied to subjects naïve to mecasermin from Study 1419 (applicant's Table 11.3.2-2). In patients followed for up to 3 years of mecasermin treatment, HVSDS increased from  $-3.4 \pm 1.5$  at baseline to  $2.5 \pm 2.3$  (Year One),  $-0.0 \pm 1.4$  (Year 2), and  $0.6 \pm 2.3$  (Year 3); all the increases from pre-dose were statistically significant.

Table 11.3.2-2: Annual Height Velocity Standard Deviation Scores (Subjects in Study 1419 Naïve to Mecasermin)

	Pre-dose	Year 1	Year 2	Year 3
<b>Subjects Completing ≥ 1 Year</b>				
N	35	35		
Mean (SD)	-3.6 (1.6)	2.1 (2.1)		
Median	-3.7	1.9		
Min, Max	-6.6, -0.5	-4.4, 5.5		
Mean (SD) for change from pre-dose	N/A	5.7 (2.8)		
P-value for change from pre-dose [1]	N/A	<0.0001		
95% CI for change from pre-dose	N/A	(4.8, 6.7)		
<b>Subjects Completing ≥ 2 Years</b>				
N	25	25	25	
Mean (SD)	-3.8 (1.3)	2.4 (1.9)	-0.1 (1.7)	
Median	-3.6	2.2	-0.0	
Min, Max	-6.6, -1.5	-1.4, 5.5	-4.8, 5.2	
Mean (SD) for change from pre-dose	N/A	6.2 (2.6)	3.7 (2.3)	
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	
95% CI for change from pre-dose	N/A	(5.1, 7.3)	(2.7, 4.6)	
<b>Subjects Completing ≥ 3 Years</b>				
N	15	15	15	15
Mean (SD)	-3.4 (1.5)	2.5 (2.3)	-0.0 (1.4)	0.6 (2.3)
Median	-2.9	2.2	-0.0	0.7
Min, Max	-6.6, -1.5	-1.4, 5.5	-3.5, 2.0	-3.6, 5.5
Mean (SD) for change from pre-dose	N/A	5.9 (2.9)	3.4 (1.9)	4.0 (2.5)
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	<0.0001
95% CI for change from pre-dose	N/A	(4.3, 7.5)	(2.3, 4.5)	(2.6, 5.4)

[1] P-values for comparison versus pre-dose values are computed using paired t-tests  
 N/A: Not available

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The applicant reports that only 5 patients in the clinical trials had a first year HV below 5 cm/yr. They are listed in Table 5. Three of them were treated for 8-9 years and had increases in height SDS of 1, 1.3 and 2, respectively. One of them (patient 10-917)

grew poorly despite an initial first year response (albeit modest). Another one (patient 10-049) did not respond during the first year of treatment.

**Table 5: Subjects with First Year Height Velocities < 5 cm.**

Subject ID	Baseline HV (cm/yr)	First Year HV (cm/yr)	Comments
10-049	4.6	1.8	Discontinued early in Year 2 for non-compliance.
18-008	2.7	2.4	At age 18 (after approx. 8 years later) increased height SDS by 1.3 and has further growth potential based on bone age.
18-011	1.0	3.8	After approx. 9 years of treatment had a height SDS increase of 2. Baseline IGF-1 SD score was -2.8; during treatment the mean IGF-1 SD score was -1.9 (range -3.6 to 0.1).
18-009	1.9	4.5	After approx. 9.5 years of treatment had a height SDS increase of 1.
10-917	1.3	4.9	Grew poorly for the next 2 years (HV 2.7 cm and 2.5 cm during Year 2 and Year 3) and had a decrease in height SDS from baseline. Investigator noted that “perhaps a nutritional deficit was present in addition to a GHR defect” (BMI SDS decreased from 1.5 at baseline to 0.2 at last visit).

Source: text in Section 5.3.5.2.4

## Secondary Efficacy Analyses

### Height SDS

Mean height SD scores (and changes from baseline) for Year 1 through Year 8 are presented in Table 6. The mean height SD score changed from -6.7 at baseline to -5.9 at the end of Year 1 of mecasermin treatment; this finding was statistically significant (p

< 0.0001). For the following years (Years 2 through Year 8) the mean height SDS increased to -5.6, -5.4, -5.5, -5.6, -5.4, -5.2, and -5.2 (all were statistically significant relative to baseline height SDS). The height SDS changes relative to baseline that were observed on treatment were 0.8 (Year 1), 1.2 (Year 2), 1.4 (Year 3), 1.3 (Year 4), 1.4 (Years 5 through 7), and 1.5 (Year 8); most of the increase in height SDS was achieved by Year 3 and was maintained through Year 8.

**Table 6: Annual Height Standard Deviation Scores by Number of Years treated with Mecasermin**

Statistics	Year 1 (N=61)	Year 2 (N=51)	Year 3 (N=40)	Year 4 (N=24)	Year 5 (N=21)	Year 6 (N=20)	Year 7 (N=16)	Year 8 (N=13)
Mean (SD)	-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)
Median	-5.8	- 5.6	-5.5	-5.6	-6.0	- 6.2	- 5.6	-5.2
Range	-10.7,- 2.2	-9.5, -2.0	-8.8, -2.0	-8.7, -1.7	-8.4, -1.5	-8.2, -1.0	-8.3, -1.1	-8.7, -1.5
Change*	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)
p-value**	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0001	0.0003
95 % CI***	0.7, 0.9	0.9, 1.4	1.1, 1.7	0.8, 1.9	0.8, 2.0	0.8, 1.9	0.8, 1.9	0.9, 2.2

\*Mean (SD) for change from pre-dose.

\*\* Paired t-test for change from pre-dose.

\*\*\* CI = confidence interval for change from pre-dose

Source: Table 11.3.2-1 in 5.3.5.2.4 Study report 1419.

The height SD score data for the group of patients who were naïve at the time of enrollment in study 1419 are presented in applicant’s Table 11.4-2. The results, presented for 3 years of treatment, are similar to those observed for the whole patient population studied. Specifically, at the end of Year 3, the height SDS change was  $1.6 \pm 0.9$  (naive patients in 1419) vs.  $1.4 \pm 1.1$  (all patients group).

Table 11.4-2: Annual Height Standard Deviation Scores (Study 1419 Subjects Naïve to Mecasermin Treatment)

	Baseline	Year 1	Year 2	Year 3
<b>Subjects Completing ≥ 1 Year</b>				
N	38	38		
Mean (SD)	-6.5 (1.7)	-5.7 (1.6)		
Median	-6.5	-5.6		
Min, Max	-10.7, -3.2	-9.5, -2.7		
Mean (SD) for change from pre-dose	N/A	0.8 (0.5)		
P-value for change from pre-dose [1]	N/A	<0.0001		
95% CI for change from pre-dose	N/A	(0.7, 1.0)		
<b>Subjects Completing ≥ 2 Years</b>				
N	28	28	28	
Mean (SD)	-6.6 (1.8)	-5.7 (1.8)	-5.4 (1.9)	
Median	-6.5	-5.3	-5.2	
Min, Max	-10.7, -3.2	-9.5, -2.7	-8.9, -2.0	
Mean (SD) for change from pre-dose	N/A	0.9 (0.5)	1.2 (0.7)	
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	
95% CI for change from pre-dose	N/A	(0.7, 1.1)	(0.9, 1.5)	
<b>Subjects Completing ≥ 3 Years</b>				
N	17	17	17	17
Mean (SD)	-6.6 (1.5)	-5.7 (1.7)	-5.4 (1.7)	-5.1 (1.7)
Median	-6.4	-5.4	-5.2	-4.6
Min, Max	-10.7, -4.4	-9.5, -3.2	-8.9, -2.8	-8.3, -2.3
Mean (SD) for change from pre-dose	N/A	0.9 (0.5)	1.2 (0.8)	1.6 (0.9)
P-value for change from pre-dose [1]	N/A	<0.0001	<0.0001	<0.0001
95% CI for change from pre-dose	N/A	(0.6, 1.2)	(0.8, 1.6)	(1.1, 2.0)

[1] P-values for comparison versus pre-dose values are computed using paired t-tests  
 N/A: Not available

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## Other efficacy analyses

### Analysis of subjects without baseline height velocity data

The applicant reports first year efficacy results for the three subjects for whom baseline HV information were not available and who, therefore, were excluded from the primary efficacy analysis. The efficacy data for these patients is presented in applicant's Table 1.5-1. The Year 1 height velocities (10.3, 6.4 and 9.3 cm/yr., respectively) were all above the mean baseline HV of 2.8 cm/yr and comparable to the Year 1 mean HV of 8.0 cm/yr observed for the 58 subjects of the primary analysis. The changes in height SDS at the end of the first year of treatment were 0.3, 0.3 and 0.7, respectively. All three patients have been treated beyond Year 1 (4, 1 years, 3 years, 2.4 years respectively) and exhibited further increases in height SDS (relative to baseline) of 1.4, 1.4 and 1.0 respectively. Overall, this analysis suggests that the three patients excluded from the primary analysis appear to have responded on treatment.

**Table 11.5-1: Year One Efficacy Results for Subjects without Baseline Height Velocity**

Subject	10-911	10-941	10-942
Status	Ongoing	Ongoing	Ongoing
Age (years)	14.8	3.2	1.3
Gender	M	F	M
Baseline Height (cm)	115.8	67.0	66.7*
Baseline Height SD Score	-5.5	-7.7	-5.5*
Year One Height Velocity (cm/yr)	10.3	6.4	9.3
Year One Height SD Score	-5.2	-7.4	-4.8
Change in Height SD Score	0.3	0.3	0.7
Last Age (years)	18.9	6.2	3.7
Last Height SD Score	-4.1	-6.3	-4.5
Total Change in Height SD Score	1.4	1.4	1.0

\*The first post-baseline height and its SD score are used since baseline height is missing.

### Subjects with less than one year of efficacy data

Ten subjects received mecaseimerin treatment for less than one year during Study 1419 and were all excluded from primary analysis of HV. Of these, 7 subjects were previously treated with Pharmacia's rhIGF-I and data prior to enrollment to Tercica's clinical study were not available. Three other subjects have been in the study for less than one year (their participation to Study 1419 varied in duration from 0 to 0.7 year). Interim on-trial efficacy data for all ten patients are provided in Table 11.6-1. All but one subject had increases in height SDS which ranged from 0.1 to 0.7.

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**Table 11.6-1: Efficacy Results for Subjects With Less Than One Year of Mecasermin Treatment**

Subject	10-943	10-945	10-947	10-948	10-953	10-954	10-955	10-956	10-957	10-958
Previous Mecasermin Therapy	N	Y	Y	Y	N	Y	Y	N	Y	Y
Ongoing	N	Y	Y	Y	Y	Y	N	Y	Y	Y
Baseline Age (yrs)	11.3	15.9	12.2	11.6	12.5	16.6	17.1	17.5	5.6	8.2
Gender	M	F	F	F	M	M	M	M	M	F
Baseline Height Velocity (cm/yr)	1.2	1.2	2.6	3.6	3.2	N/A	5.2	NA	1.3	7.9
Baseline Height (cm)	96.2	128.6*	126.4	114.2	100.6	138.8*	151.4	145.2	NA	N/A
Baseline Height SD Score	-7.6	-5.3*	-3.5	-4.5	-7.4	-4.6*	-3.2	-4.0	NA	N/A
Time on Treatment (yr)	0.7	0.5	0.5	0.4	0.0	0.5	0.5	0.7	0.0	0.0
Last Height (cm)	100.0	129.1	129.4	117.2	N/A	140.4	154.6	151.7	N/A	N/A
Change in Height (cm)	3.8	0.5	3.0	3.0	N/A	1.6	3.2	6.5	N/A	N/A
Last Height SD Score	-7.3	-5.2	-3.6	-4.4	N/A	-4.5	-2.9	-3.3	N/A	N/A
Change in Height SD Score	0.3	0.1	-0.1	0.1	N/A	0.1	0.3	0.7	N/A	N/A

\* First post-baseline height and height SD score since baseline height was missing  
 N/A: Not available

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### Non-compliant patients

The applicant reports that 4 subjects were discontinued from the study for non-compliance. The data suggest that, with the exception of one patient, the all other 3 subjects who were non-compliant responded to treatment. Specifically, patients 10-902, 10-910, and 18-001 were reported as having had “good increments in first year height velocity and improved their HTSD score at termination by 1.4, 2.6 and 1.2, respectively.” Indeed, as illustrated in Table 7, these patients exhibited annual height velocities in excess of those noted before treatment initiation and continued treatment for a considerable length of time. One patient (10-949) failed to improve both his first year height velocity and height SD score at study termination.

**Table 7: Efficacy data (height velocity) for 4 subjects who were discontinued for non-compliance**

Time of	Patient 10-902	Patient, 10-910	Patient 18-001	Patient 10-949
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Clinical Review  
 {Dragos Roman}  
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 {Increlex (mecasermin)}

evaluation	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS
Baseline	2.7	-3.7	1.4	-3.0	2.0	-4.4	4.6	-1.1
Year 1	9.1	3.0	5.3	-0.1	6.4	0.4	1.8 <sup>^</sup>	-4.4
Year 2	6.8	1.0	6.6	-0.2	4.4	-1.6	N/A	N/A
Year 3	4.8	-1.0	6.2 <sup>**</sup>	-0.3	2.9	-3.2	N/A	N/A
Year 4	4.2	-1.6	N/A	N/A	2.8	-3.3	N/A	N/A
Year 5	4.6	-0.8	N/A	N/A	2.1	-3.8	N/A	N/A
Year 6	4.2 <sup>*</sup>	-0.9	N/A	N/A	4.1	-0.8	N/A	N/A
Year 7	N/A	N/A	N/A	N/A	4.9	-0.2	N/A	N/A
Year 8	N/A	N/A	N/A	N/A	5.7	-0.4	N/A	N/A
Year 9	N/A	N/A	N/A	N/A	7.4 <sup>***</sup>	0.1	N/A	N/A

\* Last calculated height velocity, at Year 6.8: HV = 3.7 cm/yr and HVSDS = -1.1.

\*\* Last calculated height velocity, at Year 3.9: HV = 3.1; HVSDS = -0.9.

\*\*\* Last calculated height velocity, at Year 9.9: HV = 6.6; HVSDS = 0.6.

<sup>^</sup> Last calculated height velocity, at Year 1.

Source: Integrated patient profiles.

### Subjects lost for follow-up

As illustrated in Table 8, four out of the five subjects lost for follow-up (patients 10-903, 10-907, 18-002 and 18-005), exhibited first year increases in HV above baseline. In two cases they were quite considerable (9.8 and 11.3 cm, respectively); in two other patients they were modest (5.5 cm each). One subject (10-943) did not have one full year of treatment but the HV available at 0.7 years indicated an increase of 4.6 cm over baseline. All subjects showed improvements in height SD scores by 2.2, 3.7, 0.3, 1.4 and 0.4, respectively.

Table #: Efficacy data (height velocity) for 5 subjects who were lost for follow-up

Time	Patient ID									
	10-903		10-907		10-943		18-002		18-005	
	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS
Baseline	3.6	-1.7	2.0	-4.3	1.2 <sup>^</sup>	-4.4	2.7	-1.6	4.9	-1.8
Year 1	9.8	4.2	11.3	6.0	N/A	N/A	5.5	-0.8	5.5	-1.0
Year 2	7.2	0.9	8.2	3.1	N/A	N/A	6.5	0.3	3.8	-2.5
Year 3	4.5	-1.1	7.0	2.1	N/A	N/A	5.8	1.0	2.8	-3.5

Year 4	5.2	-0.8	7.7	3.2	N/A	N/A	6.2	3.9	4.2	-1.6
Year 5	5.5	0.3	6.4	1.6	N/A	N/A	4.6	N/P	2.9	-3.2
Year 6	5.0	1.3	6.0**	1.1	N/A	N/A	4.3^^	N/P	2.7	-3.1
Year 7	3.6*	3.2?	N/A	N/A	N/A	N/A	N/A	N/A	2.7	-2.3
Year 8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.7#	-1.5

N/P = not presented. N/A Not available in the Integrated profile section.

\*Last recorded visit with height measured, at Year 7.8: HV = 4.3; HVSDS = not provided.

\*\* Last calculated height velocity, at Year 6.

^Patient discontinued trial at 0.7 Years of treatment.

^^ Last calculated height velocity, at Year 6.

# Last calculated height velocity, at Year 8.

Source: Integrated patient profiles

### Other subjects who discontinued before reaching adult height

Two additional patients (10-925, and 10-955) discontinued study 1419 for reasons other than “non-compliance” or being “lost for follow-up.” One discontinued for “poor growth” and one for “parent/subject decision”, respectively. One additional patient (18-007) participated in an early study but did not enroll in study 1419. The efficacy data (height velocity) for all three patients are displayed in Table 9. Patient 10-925 (who discontinued for “poor growth”) had an above-baseline response during the first two years of treatment (12.3 and 8.4 cm., respectively) and a poor response relative to baseline during the third year. Patient 10-955 (who discontinued for parent/patient decision) had only baseline data available. Patient 18-007 had a variable response to treatment (HV acceleration during the Year 1 and HV slightly below baseline for the next two years).

Table 9: Efficacy data (height velocity) for 3 additional subjects who did not reach near-final height

Time of evaluation	Patient 10-925		Patient 10-955		Patient 18-007	
	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS	HV (cm/yr)	HVSDS
Baseline	4.9	-2.2	5.2**	1.8	5.1	-0.7
Year 1	12.3	4.5	N/A	N/A	8.2	3.5
Year 2	8.4	1.9	N/A	N/A	4.9	-0.4
Year 3	4.8*	-1.4	N/A	N/A	4.7	-0.4

Year 4	N/A	N/A	N/A	N/A	6.2*	1.2
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N/A Not applicable.

\* Last calculated height velocity.

\*\* The only available height velocity.

Source: Integrated patient profiles.

## Near-Adult Height

Near-adult height was defined as the height associated with a bone age  $\geq 16$  years for boys and  $\geq 14$  years for girls. Three subjects (10-904, 18-010, and 18-013) attained near-adult height by the aforementioned criteria (applicant's Table 11.12-1). Three additional patients (10-901, 10-905, and 18-004) are also included in the near-adult height efficacy analysis on the basis that they were "considered by the investigators to have completed the intended course of treatment to near adult height." These patients had bone ages close to the aforementioned criteria; specifically, two female patients had bone ages close to 14 years (13.5 years) and a male subject had a bone age slightly below 16 years (15.6 years).

For this 6 subject subgroup, the applicant calculates a mean difference between the observed heights at the end of treatment and the expected heights (using the 50<sup>th</sup> percentile for adult heights from published growth curves<sup>78</sup> specific for Laron Syndrome) of  $16 \pm 8$  cm. Patients in this dataset were treated for periods of time ranging between 5.4 and 9.9 years. Using the same methodology, the estimated individual height gains were 3, 11, 17, 19, 23, and 23 cm, respectively.<sup>79</sup> Three subjects (18-004, 18-010, and

<sup>78</sup>Z. Laron, P Lilos, B Klinger: Growth curves for Laron syndrome. Archives of Diseases in Childhood 1993; 68: 768-7.

<sup>79</sup>The two subjects who displayed the poorest height gain within this cohort (patient 10-904: 11 cm height gain, and patient 10-905: 3 cm height gain) were twins who exhibited a complicated clinical picture which included congenital communicating hydrocephalus and severe lipohypertrophy at the injection site. The extent to which these comorbidities may have contributed to the limited long-term benefit cannot be quantified.

18-013) also received Lupron treatment for 27, 34, and 51 months respectively; the effects of Lupron and mecaseimerin in these patients cannot be dissociated.

**Table 11.12-1: Subjects Who Attained Near Adult Height**

Subject	10-901	18-004	18-010	18-013	10-904	10-905
Gender	M	F	F	M	F	F
Time on Study (years)	7.7	9.9	5.4	8.4	6.6	6.6
Last Age (years)	17.4	14.9	20.6	21.4	14.8	14.8
Estimated Last Bone Age (years)	15.6	13.5	15.0	17.0	14.5	13.5
Change in Height During Treatment (cm)	53.4	57.5	26.0	42.6	36.1	28.4
Approximate Expected Change in Mean Height (cm) for Age and Gender for Untreated IGFD Subjects From Laron [21]	30	40	3	24	25	25
Approximate Difference Between Observed and Expected Change in Height (cm)	23	17	23	19	11	3

### Efficacy in subjects with and without antibodies to IGF-1

The applicant reports that there is no difference statistically in mean Year 1 height velocities between antibody-positive and antibody-negative patients (p-value = 0.62; see

**Table 11.14-1: First Year Results for Subjects with and without Antibodies to IGF-1**

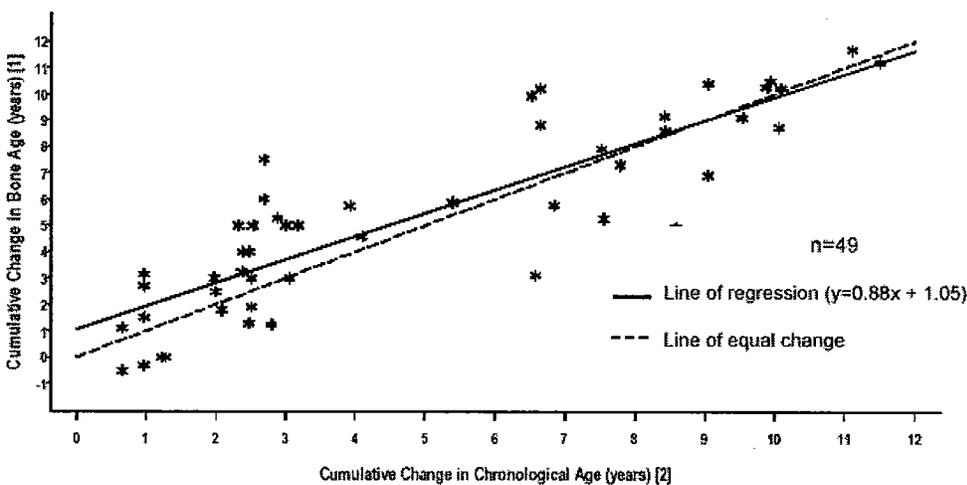
	Subjects without Antibodies (n=11)	Subjects with Antibodies (n=11)
Females, Males (n)	3, 8	4, 7
	Mean ± SD (range)	Mean ± SD (range)
Baseline Age (years)	7.4 ± 4.6 (1.7 to 15.2)	6.3 ± 3.8 (2.3 to 13.5)
Height Velocity (cm/yr)	7.3 ± 3.1 (2.4 to 12.8)	7.9 ± 2.1 (5.3 to 11.3)

also applicant's Table 11.14-1).

## Bone age changes

The applicant presents an analysis of the change in bone age versus the change in chronological age during mecasermin treatment (Figure 11.9.1). The analysis includes 49 patients who had a baseline bone age evaluation and a second bone age evaluation after at least one year of treatment.<sup>80</sup> The mean change in bone age was  $5.3 \pm 3.4$ ; the mean change in chronological age was  $4.9 \pm 3.4$  and the difference between the two was  $-0.5 \pm 1.8$  ( $p=0.070$ ). The analysis suggests that the mean change in bone age is comparable to the mean change in chronological age. It should be recognized that patients with primary IGFD have a delay in bone age relative to chronological age and that bone age is expected to change somewhat faster than chronological age on treatment.

Figure 11.9-1: Cumulative Change in Bone Age versus Change in Chronological Age (Subjects Naïve to Mecasermin)



- [1] Change from first bone age assessment to last bone age assessment  
[2] Change in age from time of first bone age assessment to time of last bone age assessment

<sup>80</sup> Eight of the 49 patients received treatment with Lupron in order to arrest puberty; such treatment was as short as 4 months and as long as 51 months.

## Use of Lupron

Lupron (an LHRH agonist) has been used to delay puberty and subsequently to decrease the rate of bone age progression in 11 subjects ((10-906, 10-908, 10-910, 10-911, 10-950, 10-951, 10-954, 10-956, 18-004, 18-010, and 18-013; one of them (10-908) started Lupron only prior to the NDA submission and no efficacy data re available for him/her). Efficacy data for 10 Lupron-treated patients are presented in applicant's Table 11.11-1. The duration of Lupron treatment ranged between 4 and 51 months. Ages at onset of Lupron treatment ranged between 11.5 years and 16.6 years. Lupron plus mecaseimerin increased height SDS in only 3 patients by 2.4, 1.4 and 1.4 respectively in patients treated for 34, 50, and 51 months, respectively. These were the patients with the longest exposure to the treatment. One patient was treated with Lupron for 31 months without any apparent benefit in height SDS.

Table 11.11-1: Subjects Who Received Lupron®

Subject	10-906	10-910	10-911	10-950	10-951	10-954	10-956	18-004	18-010	18-013
Ongoing Lupron® therapy	Y	N	Y	Y	Y	N/A**	N/A**	N	N	N
Gender	M	M	M	M	F	M	M	F	F	M
Baseline Height SD Score	-6.6	-9.3	-5.5	-4.2	-6.6	-4.6*	-4.0	-3.4	-12.1	-7.5
Age at which Lupron® was started (years)	11.5	15.2	14.8	15.9	11.8	N/A	15.9	11.9	16.8	14.0
Approx. Height SD Score at Lupron® Start	-2.7	-6.3	-5.5	-4.0	-6.0	N/A	N/A	-1.0	-10.2	-6.2
Approx. Height SD Score at Lupron® End or at Last Evaluation	-2.7	-6.7	-4.1	-4.0	-5.8	-4.5	-3.3	-1.8	-7.8	-4.8
Approx. Time on Lupron® (Months)	31	9	50	4	4	N/A	N/A	27	34	51
Change in Height SD Score during Lupron®	0.0	-0.4	1.4	0.0	0.2	N/A	N/A	-0.8	2.4	1.4

N/A denotes that data were not available, e.g., for subjects for whom post-baseline data have not yet been received.

\* Indicates that the first post-baseline height was used in computing the baseline height SD score because the baseline height was missing for this subject who was already taking Lupron® while receiving Pharmacia rhIGF-1 prior to enrollment in Study 1419.

\*\* Indicates that the subject received Lupron® prior to enrollment in Study 1419 with unknown date of discontinuation.

### 6.1.5 Clinical Microbiology

Mecasermin is not an antimicrobial. Therefore this section of the review template does not apply to mecasermin.

### 6.1.6 Efficacy Conclusions

Mecasermin treatment was effective in increasing linear growth in patients with severe primary IGFD at doses of 80-120 µg/kg BID. Mecasermin more than doubled the mean height velocity in the first year of treatment and induced a distinct “catch-up” growth phenomenon. Although subsequently the mean HV decreased, it remained at levels above those present at baseline.<sup>81</sup> Mean height SDS (which compares the patients’ heights to those of the normal population across ages and gender) improved steadily for 3 years and was maintained for the next 5 years; it was statistically significantly higher than baseline mean height SDS over 8 years of treatment. Preliminary data in a few patients suggest that gains in final height can be substantial. When judged in the context of linear growth obtained with other products (specifically GH), the linear growth observed with rhIGF-I (mecasermin) is slower than that observed in GH deficiency and comparable to that observed in idiopathic short stature during the first year of treatment.<sup>82</sup>

## 7 INTEGRATED REVIEW OF SAFETY

Although mecasermin has been administered as an investigational drug to a variety of patients, this safety review focuses on the 71 patients who represent the primary IGFD clinical program. Therefore, unless otherwise specified, all statements in this review apply exclusively to patients with primary IGFD who have been treated with mecasermin. Mecasermin has been administered as an investigational drug also to patients with Type 1 diabetes (>500 subjects), Type 2 diabetes

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<sup>81</sup> Mean height velocity (cm/yr) for the first 6 years of treatment and mean height velocity SDS for the first 7 years of treatment were statistically greater than the mean baseline height velocity.

<sup>82</sup> For idiopathic short stature the height velocity at one year is approximately 8-9 cm/yr (change from baseline 4-5 cm/yr) for doses of 0.24/0.37mg/kg/week (source: Humatrope review); for a dose of 0.3 mg/kg/week the one year HV was  $7.5 \pm 1.2$ cm/year and the baseline subtracted change was  $3.1 \pm 1.7$  cm/yr. (source: Nutropin review). One-year height velocity in patients with GH deficiency ranges between 7.5 and 13.5 cm/yr (average approximately 10 cm/yr) depending on the dose used (baseline subtracted change in HV is around 8-10 cm/yr)

(> 700 patients), HIV cachexia (11 patients) and other patient populations in 30 investigator-sponsored studies. With the exception of serious adverse events (SAEs) these datasets are not analyzed in detail.<sup>83</sup>

## 7.1 Methods and Findings

### 7.1.1 Deaths

There were no deaths reported during the primary IGFD studies.<sup>84</sup>

### 7.1.2 Other Serious Adverse Events

Six serious adverse events were reported by 4 subjects (all SAEs occurred during study F0671g). The nature of the SAEs as well as the investigator's assessment as to whether they were related or not to mecasermin treatment, are presented in Table 10. Three out of 6 SAEs were deemed "possibly related" to the mecasermin treatment by investigators. They were "tonsillar hypertrophy and adenotonsillectomy" in a 14-year-old male with a history of sleep apnea, tricuspid insufficiency (diagnosed by

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<sup>83</sup> With few exceptions, the patient population in the diabetes studies is mainly adult, while the primary IGFD population is exclusively pediatric. The route of administration in several of these studies is intravenous (unlike the route of administration for this application which is subcutaneous). Finally, and importantly, the adverse event profile for Type 1 and Type 2 diabetes and for HIV patients is influenced in such a fundamental way by the specifics of these diseases and coexisting morbidities that it cannot be extrapolated to children with primary IGFD.

<sup>84</sup> There were three deaths in the diabetes program, none attributable to mecasermin: cardiopulmonary arrest, head injury, and myocardial infarction. They were described as follows: "A placebo treated 67-year old woman with a 27-year history of Type 1 diabetes died of cardiopulmonary arrest secondary to advanced cardiovascular disease. A 47-year old man with Type 2 diabetes died as the result of severe head injuries sustained after being struck by a motor vehicle. A 67-year old woman with Type 2 diabetes died 6 weeks after completing the study due to a myocardial infarction." An additional death occurred in the severe insulin resistance program in a 13-year old male with Leprechaun syndrome (a syndrome that is characterized by severe growth failure, early death, and severe insulin resistance due to genetic mutations of the insulin receptor); this patient was treated with a dose of 400 µg/kg twice daily. The patient died during sleep. The applicant states that "the exact cause of death has not been reported, nor has the status of his mecasermin use in the weeks prior to his death been confirmed."

echocardiogram in an otherwise asymptomatic patient),<sup>85</sup> and a seizure in a five year-old which may have been associated with hypoglycemia. All other SAEs were judged as “unrelated” to study drug by the investigators.

**Table 10: Serious Adverse Events**

Patient I.D.	Adverse Event	Relationship to study drug*
10-903	tonsillar hypertrophy and adenotonsillectomy.	possibly related
10-906	severe pneumonia and empyema	unrelated
18-001	tricuspid insufficiency (echocardiogram result)**	possibly related
18-001	generalized seizure***	unrelated
18-009	febrile seizures associated with a tooth abscess****	possibly unrelated
18-009	skull fracture related to trauma.	unrelated

\*In investigator’s opinion, based on information from the study report for Study F0671.

\*\*According to the narrative, at study discontinuation an echocardiogram showed “moderately severe tricuspid insufficiency and right ventricular hypertrophy” (a grade II/IV murmur was reportedly noted early in the trial at Months 6, 12, and 24). ECG was reported as normal. Pediatric cardiology evaluation reported “ a grade II/IV systolic murmur and diagnosed possible pulmonary artery hypertension [..].”

\*\*\*The patient had a history of seizure disorder “treated intermittently” with Tegretol.

\*\*\*\*The narrative states that: “the subject [...] did not have a history of seizures. The subject had a mildly severe fever and a moderately severe tooth abscess at the time of the event; it was unclear to which condition the seizure was related. It was hypothesized that the subject’s dental caries could have resulted in inadequate nutrition and a subsequent hypoglycemic seizure.”

Five additional SAEs in four patients were reported in the 120-day safety update. The nature of the SAEs as well as the investigator’s assessment as to whether they were related or not to mecasermin treatment, are presented in Table 11. Of these three were considered possibly related to the study drug: (1) an episode of loss of consciousness and seizure like-activity in a 13 year-old male which responded to glucagon injection; (2)

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<sup>85</sup> The event was diagnosed 4.9 years on treatment at age 11 years. The patient discontinued after 9.9 years of treatment for non-compliance. The narrative states that the subject “was noted to have a clinically abnormal echocardiogram after 5 years of treatment with mecasermin. Specifically, tricuspid insufficiency and right atrial and right ventricular enlargement were noted. The left ventricular chamber size, mass and systolic function were reported to be normal. Serial echocardiograms performed at 6 to 18 months intervals for approximately 5 additional years did not reveal any significant change in cardiac function over time.”

renal calculi/colic in a 14 year-old with known history of hydronephrosis and kidney stones; (3) headache, papilledema, Arnold-Chiari malformation in a 9 year-old male (patient discontinued the study drug),

**Table 11: Serious Adverse Events in the 120-day Safety Update**

Patient I.D.	Adverse Event	Relationship to study drug*
18-011	Loss of consciousness/seizure-like activity**	Possibly related
18-011	Renal calculus**	Possibly related
18-012	Appendicitis**	Not related
57-0003	Gastroenteritis/dehydration***	Not related
57-0004	Papilledema/Headache/Arnold-Chiari malformation***	Possibly related

\*In investigator's opinion.

\*\* Patients enrolled in Study 1419.

\*\*\* Patients enrolled in Study MS301.

Several SAEs reported in the Type 1 and Type 2 diabetes mecasermin program were considered treatment-related. In the Type 1 diabetes study F0695 they were “progression of retinopathy,” “severe hypoglycemia,” “hypoglycemia,” “abnormal stress test (ST segment depression),” and “optic nerve head neovascularization.” In the Type 1 diabetes study F0708g they were “hypoglycemia” or “symptomatic hypoglycemia” (a total of 4 subjects).<sup>86</sup> In the Type 2 diabetes studies adverse events considered by the investigators to be treatment-related were congestive heart failure (2 subjects), tachycardia, diverticulitis, peritonitis, chest pain (2 subjects), back pain (2 subjects), diabetic amyotrophy, convulsions NOS, electrocardiogram changes, lung nodule biopsy, and pulmonary edema. An additional treatment-related SAE was reported in a healthy volunteer during a Phase I clinical pharmacology study (severe vasovagal reaction following intravenous administration of mecasermin at a dose of 0.04 mg/kg).

Several SAEs “related or “possibly -related” to mecasermin treatment were reported in the investigator-sponsored studies:

- Liver enzyme elevations (2 patients) and sleep apnea with secondary pulmonary hypertension (1 patient) in Study F0363s, which enrolled patients with non GH-deficient short stature and Laron Syndrome.<sup>87</sup>

<sup>86</sup> Two of the above-mentioned SAEs were reported in pediatric patients with Type 1 diabetes: progression of retinopathy and hypoglycemia.

<sup>87</sup> One subject, a 15-year old with GH gene deletion and a history of mild transaminase elevations, had elevation of liver enzymes on 2 separate occasions after mecasermin administration. Reportedly, at the start of treatment, he had symptoms consistent with a viral illness (ie, rash, low grade fever, and upper respiratory tract symptoms). Following mecasermin dosing of 50 µg/kg SC BID, 100 µg/kg SC BID and 200 µg/kg SC BID on three successive days the liver enzymes were elevated (on Day 3); ALT evaluations over 11 days showed the following values: 48, 217, 229, 331, and 109 (AST elevations were 66, 180, 140, 335, 76). Liver enzymes were normal on two occasions

- Syncope followed by a tonic/clonic seizure (associated with bradycardia and brief asystole) was experienced by a normal volunteer during a mecasermin/euglycemic clamp in Study F0355s.<sup>88</sup>
- Maculopapular rash in a patient during Study F0304s, which evaluated the effect of mecasermin on cachexia in AIDS wasting.

### 7.1.3 Dropouts and Other Significant Adverse Events

The applicant does not report any patient withdrawals due to adverse events.<sup>89</sup>

#### 7.1.3.1 Overall profile of dropouts

Refer to 7.13 paragraph.

#### 7.1.3.2 Adverse events associated with dropouts

Refer to 7.13 paragraph.

#### 7.1.3.3 Other significant adverse events

Hypoglycemia, liver enzyme elevation and pseudotumor cerebri, were identified as the only adverse events that required interventions. For hypoglycemia such interventions consisted in glucose/glucagon administration of lowering the dose. For liver function elevation they resulted

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after discharge. On a second admission 3 months later, mild elevation of liver enzymes was again noted at baseline; the patient received mecasermin at 50 µg/kg SC BID and further elevation of liver enzymes was noted following the third dosing (ALTs were 49, 84, 67, 475, and 35, respectively; ASTs were 63, 109, 52, 484, and 33, respectively). Mecasermin was discontinued. An extensive work-up for viral, autoimmune, and metabolic liver disease was reportedly, negative. A liver biopsy was performed and showed focal hepatocellular necrosis with a neutrophilic infiltrate (“according to the pathology report these findings were “non-specific but compatible with a medication reaction.” The events were considered to be related to mecasermin by the investigators. Another subject, a 9-year old girl enrolled in a non-GH deficient short stature study had elevation of liver enzymes on one occasion during treatment with mecasermin (this subject also had mild liver enzyme elevation at baseline with unknown etiology and also had a history of viral illness). She developed a rash and mildly elevated transaminases after 6 doses of rhIGF-I. A biopsy of the rash was consistent with a drug reaction. The subject was dropped from the study. No drug re-challenge was performed. A third subject (with Laron Syndrome, Study F0363s) had documented sleep apnea, pulmonary hypertension and cardiomegaly.

<sup>88</sup> The episode occurred at the end of a mecasermin intravenous infusion of 1.8 mg given over 10 minutes; she recovered fully without need of resuscitation (the I.V. route of administration of mecasermin was discontinued from this point forward)

<sup>89</sup> Of the 71 patients enrolled, eleven discontinued early: four (5.6 %) for non-compliance, 1 (1.4 %) for parent/subject decision, 1 (1.4 %) for poor growth, and 5 (7%) were lost for follow-up.

in clinical trial discontinuation. In one case of pseudotumor cerebri a lumbar puncture was required for reduction in cerebrospinal fluid pressure. Both hypoglycemia and pseudotumor cerebri were predicted from the beginning of the mecasermin program based on the known mechanism of action of mecasermin (i.e. secondary hypoglycemic effect) and prior experience with a related compound (growth hormone); these adverse are discussed in Section 7.1.5.5.

#### 7.1.4 Other Search Strategies

Additional search strategies employed in this review include extensive exploratory analyses in the safety datasets (SAS files). Such analyses are referred to in various sections of the safety review .

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

The safety evaluations varied somewhat across the various mecasermin clinical studies. In the early investigator-sponsored Study F0206s safety evaluations were performed monthly during the first year of therapy, bi-monthly during the second year, every 3 months during years 3 and 4, and every 6 to 12 months thereafter (visits alternated between principal investigator's site at University of North Carolina (UNC) and the referring pediatric endocrinologists). In this study patients were initially admitted in the hospital for a 19-day period during which they received dietary instructions and subsequently had the mecasermin treatment initiated and titrated from a dose of 40  $\mu\text{g}/\text{kg}/\text{dose}$  to 120  $\mu\text{g}/\text{kg}/\text{dose}$  over 2 days based on tolerability (i.e. whether they developed hypoglycemia). Serial sampling of blood glucose concentrations (before meals, at bedtime, and during the night) was conducted during this time. In subsequent studies (such as F0375g, F0632g, and F671g) the initial hospitalization time was reduced to 5 days and safety evaluations were done every 3-6 months.<sup>90</sup> Finally, in the investigator-sponsored study 1419 the frequency and intensity of safety evaluations was relaxed. Specifically, subjects referred and enrolled since 1998 by pediatric

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<sup>90</sup> Every 3 months during Studies F0375g and F0632g (both conducted at the Children's Hospital Medical Center Cincinnati (CHMCC) by principal investigator Dr. Steven Chernausk) and every 6 months during follow-up study F0671g (follow-up took place at either UNC or CHMCC).

endocrinologists internationally were seen for dose titration and follow-up by their referring pediatric endocrinologist in consultation with the principal investigator (Dr. Underwood); the applicant states that “for these subjects laboratory assessments and special study procedures are generally not available.”<sup>91</sup>

Safety assessments in the above mentioned studies included physical examinations, vital signs, intercurrent medical history, adverse events and laboratory assessments (hematology, serum chemistries, thyroid function studies, plasma or serum IGF-1 and anti-IGF-1 antibodies in the initial studies). Additional special safety assessments have been collected in some studies. They included radiograph of hand and wrist for bone age, chest X-ray, spleen and kidney ultrasounds, audiometry and tympanometry, echocardiogram, DEXA for body composition and bone mineral density, 24 hour urine creatinine, GFR by technetium scan, and mandibular cephalometric x-rays. Some of these special safety assessments were implemented after the initiation of the trial (sometimes as late as 2-3 years after starting mecasermin treatment) and baseline evaluations were not always available for comparison<sup>92</sup>.

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<sup>91</sup>Patients previously treated in Study F0671g have been seen at least annually at either UNC or CHMCC. Progress reports including interval height, weight, and reports of any adverse event were reviewed by Dr. Underwood prior to providing additional mecasermin. Several adverse events in this study were protocol-defined. They were: headache, joint disturbances, symptomatic hypoglycemia, adenotonsillar hypertrophy (sleep apnea, snoring), hearing deficit, scoliosis, behavioral changes, and changes in skin nevi)

<sup>92</sup> Laboratory assessments during the clinical program were completed at different laboratories (laboratory samples for safety assessments for F0206s were analyzed by University of North Carolina, Chapel Hill, NC; laboratory samples for safety assessments for Studies F0375g, F0632g, and F0671g were analyzed by █

█ laboratory assessments for Study 1419 were analyzed by the clinical laboratories at University of North Carolina and Children’s Hospital Medical Center (CHMCC). Samples for IGF-1 at baseline were analyzed in a number of assays. Anti-IGF-1 antibodies were analyzed at Genentech, Inc. for studies F0206s, F0375g, F0632g, and F0671g. Hand and wrist radiographs for bone age determination were read centrally by the █. Dual energy X-ray absorptiometry (DEXA) scans were read at the individual study sites, UNC and CHMCC. Ultrasounds were read centrally at the █. Echocardiograms were read at individual sites UNC and CHMCC. Assessment of mandibular cephalometric x-rays was performed at CHMCC.

The safety population includes seventy-one subjects who received at least a dose of mecasermin.<sup>93</sup>

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The relationship between “verbatim terms” and the assigned “preferred terms” was visually inspected by this reviewer across several subjects and adverse events (including SAEs) in the dataset XAE. Overall, the two types of terms used were concordant.

#### 7.1.5.3 Incidence of common adverse events

Treatment-emergent adverse events (TEAEs) are presented - by organ system- in Table 12, which reformats applicant’s Table 13.2.1-1. Forty-eight patients (68%) patients reported at least one adverse event.. The most common TEAEs reported during the study were in the following categories: “metabolic and nutritional disorders” (49%), “general disorders and administration site conditions” (41%), “respiratory, thoracic and mediastinal disorders” (39%), infections and infestations (39%) and “nervous system disorders’ (37%).

**Table 12: Adverse Events by System Organ Class**

Subjects Enrolled	n=71
Subjects Reporting At Least One Adverse Event	48 (68%)
Metabolism and Nutritional Disorders	35 (49%)
General Disorders and Administration Site Conditions	29 (41%)
Respiratory, Thoracic and Mediastinal Disorders	28 (39%)
Infections and Infestations	28 (39%)
Nervous System Disorders	26 (37%)
Gastrointestinal Disorders	23 (32%)
Ear and Labyrinth Disorders	21 (30%)
Musculoskeletal and Connective Tissue Disorders	21 (30%)

<sup>93</sup> Of these, 43 (61%) were male and 28 (39%) were female. Fifty eight (82%) were Caucasian, 3 (4%) African-American, 6 (8%) Hispanic, 3 (4%) Asian, and 1 (1%) were included in the “Other” category. Most patients (61 or 86%) had Laron Syndrome; 8 (11%) had GH gene deletion, 1 (1%) had antibodies to GH, and 1(1%) had isolated genetic GH deficiency type 1A. Sixty one (86%) of patients were Tanner I, 1 (1%) was Tanner II, and 9 (13%) had Tanner stage unknown at the beginning of treatment. Sixty four (90%) were naïve to mecasermin treatment.

Investigations	21(30%)
Skin and Subcutaneous Tissue Disorders	17 (24%)
Blood and Lymphatic System Disorders	16 (23%)
Surgical and Medical Procedures	12 (17%)
Eye Disorders	12 (17%)
Injury, Poisoning and Procedural Complications	10 (14%)
Cardiac Disorders	9 (13%)
Congenital, Familial and Genetic Disorders	8 (11%)
Psychiatric Disorders	8 (11%)
Renal and Urinary Disorders	8 (11%)
Reproductive and Breast Disorders	7 (10%)
Neoplasms: Benign, Malignant and Unspecified	1 (1%)*
Endocrine Disorders	1 (1%)
Hepatobiliary Disorders	1 (1%)
Social Circumstances	1 (1%)
Vascular Disorder	1 (1%)

\*Warts on toe

For each organ system category, the applicant provides descriptions of the most frequent adverse by “preferred term.” This is summarized next.

### Metabolism and Nutritional Disorders

The most common adverse event in this organ system category is hypoglycemia, which was reported in 30 patients (42%); the related AE hypoglycemic seizure was reported in 3 patients (4%). Hypoglycemic events are discussed in detail in a separate section of this Safety Review. Other AEs reported are hyperlipidemia (4 patients or 6%, considered “related” in 1 patient), hyperglycemia (3 patients or 4%), body fat disorder (2 patients or 3%), fat redistribution, decreased appetite NOS and obesity (all occurring in 1 patient or 1%).

### General Disorders and Administration Site Conditions

Adverse events related to the injection sites represent the most frequent AEs reported under this category (29 patients or 41%). They include lipohypertrophy (21 subjects or 30%)<sup>94</sup>, injection site bruising (5 subjects or 7%), injection site pain (2 subjects or 3%), injection site fibrosis, injection site induration, injection site skin pigment changes, injection site reaction NOS, and injection site urticaria (each in 1 patient or 1%). All the injection site AEs were considered “related” to the study medication. Other AEs reported frequently were pyrexia (15 subjects or 21%) and influenza-like illness (5 subjects or 7%). Less commonly reported AEs were chest pain, fatigue, hypertrophy NOS, mucosal membrane hyperplasia (each in 3 patients or 4%), and asthenia, chest discomfort, chest tightness, feeling cold, gait abnormal, lethargy, mucosal edema NOS (each in 1 patient or 1%).<sup>95</sup>

### Infections and Infestations

Adverse events related to “infections and infestations” were reported by 28 (39 %) of patients. The most frequent adverse events in this system organ class were upper respiratory tract infection (19 subjects or 27%), otitis media NOS (13 patients or 18%), nasopharyngitis (9 patients or 13%), tooth caries NOS (8 patients or 11%), influenza (7 patients or 10%), and pharyngitis (6 patients or 8%). Gastroenteritis NOS, respiratory tract infections NOS, tonsillitis, and viral infection NOS were reported by 5 patients each (7 %). Ear infection NOS, otitis media serous NOS, and varicella were reported in 6 patients (6%) each. A long list of infections and infestations has been reported in one or two patients each.<sup>96</sup> The vast majority of the AEs included in this system organ class

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<sup>94</sup> The applicant states that “this adverse event was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved.”

<sup>95</sup> Mucosal membrane hyperplasia, hypertrophy NOS, asthenia, chest discomfort, lethargy, and mucosal edema were all considered “related” to study medication by the investigators. Chest pain, fatigue, chest tightness, feeling cold, gait abnormal were not.

<sup>96</sup> Reported in 2 (3%) of patients were febrile infection, fungal infection NOS, molluscum contagiosum, mumps, otitis externa NOS, and pharyngitis streptococcal. Adverse events reported in only one (1%) patient were appendicitis, bronchopneumonia NOS, enterobiasis, eye infection NOS, gastroenteritis viral NOS, giardiasis, herpes simplex, hordeolum, impetigo NOS, infection NOS, lice infestation, localized infection, oral candidiasis, oral

were deemed “not related” to mecasermin by the investigators. Exceptions to this rule were AEs related to ear infections (such as otitis media, ear infection NOS, otitis media serous NOS), many of which were judged “related” to study medication.

### **Respiratory, Thoracic and Mediastinal Disorders**

Adverse events in the “respiratory, thoracic and mediastinal disorders” organ system were reported by 28 (39%) of patients. The most frequent individual AEs were snoring (17 patients or 24%) and, tonsillar hypertrophy (11 patients or 15%), almost all deemed as “related” by the investigators.<sup>97</sup> Other frequent adverse events were cough (10 patients or 14%), nasal congestion (7 patients or 10%), bronchitis NOS (6 patients or 8%), adenoidal hypertrophy, mouth breathing, pharyngolaryngeal pain, and rhinitis NOS (each 3 patients or 4%). Reported in two patients (3 %) each were dyspnea, nasal disorder NOS, and wheezing. Adverse events reported in only one patient (1%) each were asthma NOS, epistaxis, laryngitis NOS, nasal mucosal disorder NOS, nasal septum disorder NOS, obstructive airway disorder NOS, pharyngeal erythema, pulmonary hypertension NOS,<sup>98</sup> respiration abnormal NOS, rhinitis allergic NOS, and rhinorrhea.

In addition to snoring and tonsillar hypertrophy, mentioned above, other AEs considered “related” to study medication were nasal congestion (3 out of seven patients with this symptom), adenoidal hypertrophy (3/3 subjects), mouth breathing (3/3 subjects), dyspnea (1/2 subjects), nasal mucosal disorder NOS (1/1 subject), obstructive airway disorder NOS (1/1 subject), and respiration abnormal NOS (1/1/ subject).

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infection, otitis media serous chronic NOS, parotitis, scabies infestation, scarlet fever, sinusitis NOS, tooth abscess, tooth infection, and viral rash NOS.

<sup>97</sup> Specifically, all adverse events of snoring and all but one of the tonsillar hypertrophy AEs were reported as drug-related.

<sup>98</sup> The applicant states that “one subject had pulmonary hypertension diagnosed by echocardiogram following a viral bronchitis reported as an adverse event at one visit. The event was considered unrelated to study drug by the investigator and had resolved by the next follow-up visit on repeat echocardiogram.

## Nervous System Disorders

Adverse events in the “Nervous System Disorders” organ system were reported in 26 (37 %) patients. The most common were headache (20 patients or 28%), dizziness (6 patients or 8%), convulsions NOS (4 patients or 6%), and sleep apnea syndrome (3 patients or 4 %). The episodes of headache and dizziness were reported as “related” to the study drug in a large proportion of patients; many of them, according to the applicant, have been associated with hypoglycemia. Of the four episodes of convulsions, three have been associated with hypoglycemia and one with a febrile illness. All three sleep apnea episodes were deemed drug-related. The following AEs occurred in only one patient each: benign intracranial hypertension,<sup>99</sup> disturbance in attention, drooling, febrile convulsion, loss of consciousness, restless legs syndrome, somnolence, syncope, and tremor. Of these, the ones considered drug-related were benign intracranial hypertension, febrile convulsion, loss of consciousness, restless legs syndrome, and tremor.

## Gastrointestinal Disorders

There were a total of 23 (32 %) AEs in the “Gastrointestinal Disorders” group. The most common ones were vomiting NOS (14 subjects or 20%), diarrhea NOS (6 patients or 8 %), abdominal pain NOS (5 patients or 7%), “abdominal pain upper” and supernumerary teeth (each in 4 patients or 6 %), nausea, retching, tooth disorder NOS, and toothache (each in 2 patients or 3%). Adverse events occurring in only one patient were “abdominal pain lower,” dyspepsia, dysphagia, gastrointestinal upset, sensitivity of teeth, tongue papillary hypertrophy NOS, and tooth malformation. The vast majority of

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<sup>99</sup> Subject 10-915 (discussed in further section along with two other subjects: 10-904 and 10-905 who had papilledema and increased cranial hypertension).

AEs were judged as not related. About one third of the episodes of vomiting/retching were “related.”

### **Ear and Labyrinth Disorders**

Adverse events in the “Ear and Labyrinth Disorders” organ system were reported in 21 patients (30%). The most common were hypoacusis (16 patients or 23%), fluid in the middle ear (8 patients or 11 %), ear pain (6 subjects or 8%), and middle ear disorder NOS (2 patients or 3%); the large majority of them were judged treatment-related.

Adverse events reported in a single patient each were cerumen impaction, ear congestion, ear disorder NOS, otorrhea, tympanic membrane disorder NOS, tympanic membrane hyperemia, and tympanic membrane perforation; of these, ear congestion, ear disorder NOS, otorrhea, and tympanic membrane disorder NOS were considered “related”.

### **Investigations**

Twenty-one subjects (30%) had adverse events reported in the “Investigations” category. In order of decreasing frequency, the most common AEs were cardiac murmur NOS (7 patients or 10%), abnormal tympanometry (5 patients or 7%), [ab]normal echocardiogram (3 patients or 4 %), increased ALT and AST, increased blood cholesterol, and increased blood glucose (each 2 patients or 3%). Adverse events reported in only one subject each were: abnormal acoustic stimulation tests, blood in stool, decreased blood phosphorus, increased blood triglycerides, decreased bone density, irregular heart rate, increased intraocular pressure, abnormal liver function test, positive stool test for parasites and positive tuberculine test. More than half of the cardiac murmurs, all the abnormal tympanometry and echocardiogram results were considered treatment-related. One of the two increases in AST and ALT

was also considered treatment-related. All other AEs were not judged to be “related” to the treatment.

### **Musculoskeletal and Connective Tissue Disorders**

Adverse events in the “Musculoskeletal and Connective Tissue Disorders” organ system were reported by 21 (30%) of patients. The most common were arthralgia and pain in extremity (each 7 patients or 10%), back pain (5 patients or 7 %), flank pain (3 patients or 4%), limb discomfort NOS and myalgia (each 2 patients or 3%). The following AEs were reported by one patient each: contractures NOS, hip swelling, muscle cramp, musculoskeletal stiffness, neck pain, osteopenia, osteoporosis NOS, scoliosis, shoulder blade pain, soft tissue disorder NOS, and spinal deformity. Slightly over half of the cases of arthralgia and pain in extremity (lower limb pain), and all cases of myalgia were considered treatment-related, as were scoliosis, soft tissue disorder NOS, spinal deformity, muscle cramp.

### **Skin and Subcutaneous Tissue Disorders**

Seventeen (24 %) patients reported adverse events in the “Skin and Subcutaneous Tissue Disorders” category. The most frequent ones were dry skin (7 patients or 10%), acne NOS and rash NOS (5 patients each or 7 %), hyperkeratosis follicularis et parafolliculari (3 patients or 4 %), acanthosis nigricans, acrochordons (skin tags), contusion, skin hyperpigmentation, skin hypertrophy, sweating increased (2 patients each or 3%). Adverse events reported in one patient only were café au lait spots, atopic dermatitis, contact dermatitis, diaper dermatitis, dermatitis NOS, eczema, abnormal hair growth, pruritus, maculo-papular rash, papular rash, pruritic rash, seborrheic dermatitis, skin lesions NOS, and swelling face (none considered treatment-related). Except for the two patients with skin hypertrophy and one patient with skin tags, none of the above-listed AEs were considered related to mecasermin.

## **Blood and Lymphatic System Disorders**

Adverse events in the “Blood and Lymphatic System Disorders” group we reported in 16 or 23 % of patients. The most common adverse events were thymus hypertrophy (8 patients or 11 %), lymphadenopathy (4 patients or 6 %), anemia NOS and iron deficiency anemia (3 patients or 4 % each). Adverse events which occurred in only one patient were eosinophilia and thrombocytopenia. All the cases of thymus hypertrophy and one case of lymphadenopathy were considered treatment-related by the investigators; all other AEs were judged non-related.

## **Eye Disorders**

Twelve adverse events were reported in the “Eye Disorders” category. They include increased lacrimation (3 patients or 4 %), eye redness, papilledema, strabismus, and reduced visual acuity (2 patients or 3 % each), and cataract, conjunctivitis, allergic conjunctivitis, infective conjunctivitis, diplopia, and retinal disorder (one patient each). Both patients with papilledema and one of the two adverse events of reduced visual acuity were considered drug-related.

## **Surgical and Medical Procedures**

Twelve subjects (17%) had at least one surgical procedure. In decreasing order of frequency they were ear tube insertion (7 patients or 10%; the procedure performed for chronic otitis media), dental operations NOS (6 patients or 8 %), tooth extractions NOS (4 patients or 6 %), adenoidectomy (2 patients or 3 %), adenotonsillectomy, eye operation NOS, operation NOS, orchidopexy, tonsillectomy, and tooth repair (1 patient each). Of the surgical and medical procedures reported, all the seven ear tube insertions, both adenoidectomies and the one adenotonsillectomy were considered related to mecasermin treatment by the investigators.

## **Injury, Poisoning and Procedural Complications**

Ten patients (14 %) had adverse events reported in this category, which included mostly fractures, burns, and various other injuries. None of the AEs reported was considered related to mecasermin treatment by investigators.

## **Cardiac Disorders**

Adverse events in the “Cardiac Disorders” group were reported in 9 or 13% of all patients. The most common ones were tachycardia NOS and ventricular hypertrophy (3 patients or 4 % each), and cardiomegaly NOS (2 patients or 3 %). Atrial hypertrophy, mitral valve incompetence, mitral valve prolapse, palpitations, paroxysmal tachycardia NOS, and tricuspid valve incompetence were reported in 1 patient (1%) each. All cases of cardiomegaly and ventricular hypertrophy were judged treatment-related, as were the single cases of atrial hypertrophy, mitral valve incompetence, tricuspid valve incompetence, and paroxysmal tachycardia NOS. Two of the three cases of tachycardia NOS were also considered treatment-related.<sup>100</sup>

## **Congenital, Familial and Genetic Disorders**

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<sup>100</sup> The subjects were: tachycardia (10-910, 18-005, 18-008); paroxysmal tachycardia (18-004); ventricular hypertrophy (18-001, 18-011, and 10-904); atrial hypertrophy 18-008; cardiomegaly (18-004 and 18-005); mitral valve prolapse (10-91); mitral valve incompetence (18-003) and tricuspid valve incompetence (18-001).

Of the eight (11 %) of the subjects with adverse events in the “Congenital, Familial and Genetic Disorders” category, congenital jaw malformation NOS and pigmented nevus were the only AEs considered “treatment-related.” Two subjects (3%) had pigmented naevus reported as an adverse event (only one was judged related to treatment). Of the four patients with jaw malformations, three subjects (18-001, 18-009 and 18-013) were reported to have small mandibular overbite that the investigator considered related to treatment; a fourth patient (10-906) was reported to have a worsening protrusion of the mandible but was not considered treatment-related.

### **Psychiatric Disorders**

Eight subjects (11%) had one or more adverse events reported in this category. They included abnormal behavior NOS, emotional disturbance NOS, nervousness, and sleep terror (2 patients or 3 % each), attention deficit/hyperactivity disorder, bruxism, depression, disorientation, encopresis, mood swings, and stress symptoms (one patient each). Some adverse events (abnormal behavior NOS, nervousness, sleep terror, depression, and disorientation) were deemed treatment-related by the investigators.

### **Renal and Urinary Disorders**

Adverse events in the “Renal and Urinary Disorders” group were reported in 8 (13 %) patients. They were dysuria, nephrolithiasis, pollakiuria (2 patients or 3 % each), enuresis, hematuria, hydronephrosis, nocturia, renal colic, renal cysts NOS, renal pain, and urinary incontinence (one patient each). Of these, the only AEs judged to be related to treatment were nephrolithiasis, hydronephrosis, and renal colic.

### **Reproductive and Breast Disorders**

Seven (10%) adverse events were reported in the “Reproductive and Breast Disorders” category. They included gynecomastia (4 patients or 6%), hydrocele, ovarian cyst, and testicular atrophy (one patient each). Of all these adverse events only one of the gynecomastia cases was “related” to treatment.

### Other Systems

Adverse events were reported also in the following organ systems: “Endocrine Disorders”, “Hepatobiliary Disorders”, Neoplasms Benign, Malignant and Unspecified, “Social Circumstances,” and “Vascular Disorders.” None of these adverse events were reported as related to study drug.<sup>101</sup>

#### 7.1.5.4 Common adverse event tables

Table 13 lists adverse events occurring with an incidence  $\geq 5\%$  (i.e. in at least four patients) by “preferred term” in order of descending frequency across all organ systems. It summarizes applicant’s Table 16.2.11.3 from Section 5.3.3.2.4. Information on whether the events were deemed “related” by the investigator along with incidence data for such events is also included. Hypoglycemia, injection site hypertrophy, and headache were the most frequent adverse events (with a large proportion of them being treatment-related). Other frequent adverse events included signs/symptoms/conditions seen relatively frequently in the pediatric population (e.g. upper respiratory infection, pyrexia, vomiting, otitis media, influenza, etc). Several symptoms such as snoring, hypoacusis, otitis media, tonsillar hypertrophy, thymus hypertrophy, arthralgia,

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<sup>101</sup> Under Endocrine Disorders there was one case of suspected hypothyroidism treated with Synthroid for 3 months followed by discontinuation of Synthroid (the patient had a low T4 initially but free T4 and TSH were normal). Under Hepatobiliary Disorders there was one case of hepatic steatosis observed on ultrasound. Under Neoplasms Benign, Malignant and Unspecified there was a case of skin papilloma (warts on toes). Under Social Circumstances there was one adverse event of delayed puberty (“late developer”). Under Vascular Disorders there was one case of hematoma.

convulsions, gynecomastia, although seen in children in general are at the same time symptoms/conditions that can be mechanistically associated with IGF-1. The absence of a comparator or of background rates makes further interpretation difficult.

Table 13: Adverse events with an incidence  $\geq 5\%$

Adverse event	Number and (%) of patients with event N=71	Number and (%) of patients with event considered related* N=71
Hypoglycemia NOS	29 ( 41%)	28 ( 39%)
Injection site hypertrophy	21 (30%)	21 ( 30%)
Headache	20 ( 28%)	14 ( 20%)
Upper respiratory tract infection NOS	19 ( 27%)	1 ( 1%)
Snoring	17 ( 24%)	17 ( 24%)
Hypoacusis	17 ( 24%)	14 ( 20%)
Pyrexia	15 ( 21%)	0 ( 0%)
Vomiting NOS	14 ( 20%)	5 ( 7%)
Otitis media NOS	13 ( 18%)	6 ( 8%)
Tonsillar hypertrophy	11 ( 15%)	10 ( 14%)
Cough	10 ( 14%)	0 ( 0%)
Nasopharyngitis	9 ( 13%)	0 ( 0%)
Tooth caries NOS	8 ( 11%)	0 ( 0%)
Thymus hypertrophy	8 ( 11%)	8 ( 11%)
Fluid in middle ear	8 ( 11%)	5 ( 7%)
Arthralgia	7 ( 10%)	5 ( 7%)
Pain in extremity	7 ( 10%)	4 ( 6%)
Influenza	7 ( 10%)	0 ( 0%)
Ear tube insertion	7 ( 10%)	7 ( 10%)
Dry skin	7 ( 10%)	0 ( 0%)
Cardiac murmurs NOS	7 ( 10%)	5 ( 7%)
Nasal congestion	7 ( 10%)	3 ( 4%)
Bronchitis NOS	6 ( 8%)	0 ( 0%)
Pharyngitis	6 ( 8%)	1 ( 1%)
Dizziness	6 ( 8%)	4 ( 6%)

Ear pain	6 ( 8%)	4 ( 6%)
Diarrhea NOS	6 ( 8%)	0 ( 0%)
Dental operations NOS	6 ( 8%)	0 ( 0%)
Abdominal pain NOS	5 ( 7%)	1 ( 1%)
Gastroenteritis NOS	5 ( 7%)	0 ( 0%)
Respiratory tract infections NOS	5 ( 7%)	0 ( 0%)
Tonsillitis	5 ( 7%)	2 ( 3%)
Viral infection NOS	5 ( 7%)	0 ( 0%)
Influenza like illness	5 ( 7%)	0 ( 0%)
Injection site bruising	5 ( 7%)	5 ( 7%)
Tympanometry abnormal	5 ( 7%)	5 ( 7%)
Back pain	5 ( 7%)	0 ( 0%)
Acne NOS	5 ( 7%)	0 ( 0%)
Rash NOS	5 ( 7%)	0 ( 0%)
Hyperlipidemia NOS	4 ( 6%)	1 ( 1%)
Ear infection NOS	4 ( 6%)	2 ( 3%)
Otitis media serous NOS	4 ( 6%)	4 ( 6%)
Varicella	4 ( 6%)	0 ( 0%)
Lymphadenopathy	4 ( 6%)	1 ( 1%)
Tooth extractions NOS	4 ( 6%)	0 (%)
Convulsions NOS	4 (6%)	4 ( 6%)
Abdominal pain upper	4 (6%)	1 (1%)
Supernumerary teeth	4 (6%)	0 ( 0%)
Congenital jaw malformation NOS	4 ( 6%)	3 ( 4%)
Gynecomastia	4 ( 6%)	1 (1%)

\*Includes all events reported as "possible", "probable" or missing relationship to the study medication.

Source: Table 16.2.11.3 from Section 5.3.3.2.4

#### 7.1.5.5 Identifying common and drug-related adverse events

The applicant presents a separate analysis of several adverse events "of special interest." They include events that were either reported frequently or were possibly/probably related to administration of mecasermin. The list of these AEs and

their incidence during the trial is presented in applicant's Table 13.2.2-1. Several

**Table 13.2.2-1: Adverse Events of Special Interest**

<b>Adverse Event</b>	<b>Number of Subjects (%)</b>
Hypoglycemia	30 (42%)
Snoring	17 (24%)
Hypoacusis	16 (23%)
Tonsillar hypertrophy	11 (15%)
Middle ear effusions	8 (11%)
PE tube placement*	10 (14%)
Tonsillectomy/adenoidectomy	7 (10%)
Intracranial hypertension	3 (4%)
Lipohypertrophy	21 (30%)
Arthralgia	7 (10%)
Myalgia	2 (3%)

\*In 3 subjects, PE tube placement was noted in the comments of the case report form in the context of a different adverse event.

descriptive observations regarding these adverse events are subsequently presented.

### **Hypoglycemia**

The applicant reports that hypoglycemia occurred at least once in 30 (42%) subjects.<sup>102</sup> Fourteen (47%) of these thirty patients had a history of hypoglycemia.<sup>103</sup> Four subjects are reported to have had hypoglycemic seizures “on one or more occasions during treatment;” three of them also had a prior history of hypoglycemic seizures; the fourth subject was reported as having “frequent episodes of hypoglycemia generally associated with lack of adequate oral [food] intake.”

Applicant's Table 13.2.2.1-2 indicates that hypoglycemia was reported more frequently at the beginning of treatment, particularly during the first month (18 % of patients). For each of the next months of the first year hypoglycemia incidence was anywhere

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<sup>102</sup> MedDRA terms used: “hypoglycemia NOS [no otherwise specified]” and “hypoglycemia seizure.”

<sup>103</sup> For the whole cohort, eighteen subjects (25 %) are reported to have had a history of hypoglycemia prior to beginning mecasermin treatment; hypoglycemia has been described as a metabolic feature of Laron Syndrome.

between 0.0 and 6.6 %. Twenty-four percent of the episodes of hypoglycemia reported during the trial took place in the first year of mecasermin treatment.

**Table 13.2.2.1-2: Number of Reports of Hypoglycemia during each month of Mecasermin Treatment Among All Patients Treated At Least One Year (n = 61)**

Month	No. Reported	Percent
1	11	18.0
2	2	3.3
3	2	3.3
4	4	6.6
5	0	0.0
6	2	3.3
7	2	3.3
8	1	1.6
9	1	1.6
10	2	3.3
11	1	1.6
12	1	1.6

A post-hoc analysis indicates that young age, short stature and prior history of hypoglycemia may be risk factors for hypoglycemia while on mecasermin treatment.<sup>104</sup> The applicant points out that, in the judgement of the investigators “symptomatic hypoglycemia was generally avoided when a meal was consumed shortly before or after the administration of mecasermin.”

This reviewer’s analysis of hypoglycemia from the Dataset XAE adds the following observations:

- there were 4 events of hypoglycemic seizures and 121 events of hypoglycemia NOS in the dataset
- the 121 events captured under the preferred term of hypoglycemia NOS were classified as mild (60 episodes) moderate (46 episodes); severe (13 episodes); 2 episodes were classified as unknown severity
- of the patients who had hypoglycemia most patients experienced 1-3 events, some experienced more<sup>105</sup>

Table 14 summarizes some of the information related to the 13 episodes of severe hypoglycemia NOS. They appear to have occurred in relatively younger patients (less

<sup>104</sup>A comparison of patients with and without hypoglycemia during mecasermin treatment indicated that they were statistically different in the following baseline characteristics: mean height SD score (p = 0.0290), mean age (p = 0.0051) and prior history of hypoglycemia (p = 0.0018).

<sup>105</sup> Eleven patients experienced 1 event, five experienced 2 events, three experienced 3 events, one experienced 4 events, and three had 6 events each. One patient each experienced 7, 8, 9, 10, and 29 events, respectively.

than 7.4 years of age at both study doses (80 or 120 µg/kg). Although there was no apparent relationship with any particular duration of therapy, all but one occurred within 2-years of treatment initiation.

**Table 14: Severe hypoglycemia NOS**

Pt. ID	AGE (years)	Duration of IGF-I treatment	Dose (µg)	Treatment required	Hospital admission
10913	5.1	1.01	120	No	No
18001	5.8	0.04	120	Yes	No
18001	6.7	0.93	80	No	No
18001	7.1	1.34	80	No	No
18001	7.4	1.61	80	No	No
18005	6.3	1.74	100	No	No
18006	2.1	0.04	120	Yes	No
18006	2.4	0.32	120	Yes	No
18006	2.8	0.78	80	No	No
18006	3.8	1.75	80	Yes	No
18006	3.8	1.78	80	Yes	No
18009	5.5	2.88	120	No	No

Source: Dataset XAE

### Lipohypertrophy

Twenty-one subjects (30%) experienced injection site hypertrophy (lipohypertrophy). The applicant states that “in all cases, this event was associated with lack of proper rotation of injection sites and resolved when injections were properly dispersed.”<sup>106</sup>

### Tonsillar hypertrophy, snoring, otitis media, hearing abnormalities, and sleep apnea

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<sup>106</sup> The applicant states that in the early study F0206s “lipohypertrophy was most pronounced in 3 subjects who had the poorest overall growth response.” This reviewer’s visual inspection of the Dataset XAE indicates that the lipohypertrophy occurred at all doses listed. It was described as mostly “mild” in intensity, occasionally “moderate” and only in one case (patient 10905) “severe.” It occurred at variable times during mecasermin treatment (from: .23 years to 6.95 years).

The applicant provides descriptive information for several ENT adverse events captured under the following preferred terms: tonsillar hypertrophy, snoring, otitis media, hypoacusis, ear tube placement, sleep apnea. The incidence of these adverse events and specific comments (where provided) are summarized in Table 15. Although interpretation of such descriptive data is made difficult by the absence of a control group, it suggests that mecasermin treatment may be associated with hypertrophy of the adenotonsillar tissues and secondary complications such as chronic middle ear effusions (and need for fluid drainage), hearing loss, sleep apnea.

Table 15: ENT adverse events (tonsillar hypertrophy, snoring, otitis media, hearing abnormalities, sleep apnea)

Adverse event	Number of patients (incidence) and additional comments
Snoring	17 (24%)
Tonsillar hypertrophy	11 (15%); it occurred "generally during the first 1-2 years of treatment"; of these 11 subjects, nine reported hypoacusis or snoring, and six reported otitis media.
Tonsillectomy/adenoidectomy	7 (10%)
Sleep apnea	3 (4%); in all three it resolved after tonsillectomy/adenoidectomy
Middle ear effusions	8 (11%)
Otitis media NOS	13 (18%)
Serous otitis media	4 (6%)
Ear infection NOS	4 (6%)
Tympanometry abnormal	5 (7%)
Combination of serous otitis media, and/or ear infection or otitis media.	7 (10%)
Ear tubes placed	10 (14%)
Conductive hearing loss (hypoacusis)	16 (23%); it was based "primarily on audiometry"

<sup>107</sup> Audiometry and tympanometry were added when patients were well into the IGF-I clinical program (in Study F0671g) with most patients having already completed 3-4 years of treatment, (i.e. baseline tests were not available). The applicant reports that "Twenty-three subjects had 2 or more annual audiograms performed. Six subjects had normal hearing on all examinations. Eight subjects had intermittently abnormal audiograms (e.g. reported as abnormal at one evaluation and normal at another) throughout the study period. Nine subjects had abnormal

Source: Table 16.2.11.3 and text.

### **Intracranial hypertension**

Headache associated with papilledema, nausea, and vomiting was observed in 3 subjects (4%). Two of them (twin siblings with GH gene deletion) also had long-standing hydrocephalus; the symptoms resolved without treatment discontinuation. In the third patient symptoms resolved following an LP aimed at reducing cerebral spinal fluid pressure.

### **Edema, arthralgia, myalgia**

The applicant states that “there were no reports of edema, peripheral edema, or carpal tunnel syndrome.” Arthralgia (reported as joint pain, knee pain, or intermittent knee or leg pain) was reported in 7 subjects (10%). Myalgia (muscle aches) was reported for 2 subjects (3%).

### **Tumorigenesis**

There were no reports of cancer during mecasermin treatment in children with primary IGFD..

### **Retinopathy**

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audiograms at all exams including one subject who had profound deafness prior to treatment and wore hearing aids. All of the subjects with abnormal audiograms were noted to have mild or moderate conductive hearing loss except the one subject who was known to have profound hearing loss prior to treatment.” Occasionally conductive hearing loss in other subjects was associated with otitis media at the time of an exam and a subsequent audiogram was determined to be normal.

Patients are reported to have undergone funduscopy examinations at baseline and periodically during treatment as part of the routine physical examination. The applicant states that “there were no reports of retinopathy or loss of vision during the study for any subject.”<sup>108</sup>

### **Adverse events of special interest in Type 1 and Type 2 Diabetes**

The applicant provides an analysis of the adverse events of interest identified in primary IGFD, conducted in subjects with Type 1 and Type 2 diabetes who were exposed to mecasermin (Table # 2.7.4.2.2-1). In these studies the duration of exposure to mecasermin was mostly limited to < 3 months; several subjects completed more than 8 months (one study - F0708, which originally designed as a one-year study). In pediatric diabetic patients (most of whom had Type 1 diabetes), mecasermin treatment was associated with a higher incidence of injection site hypertrophy (14.7% vs. 9.1% in placebo group). Similarly there was also a higher incidence of otitis media in these patients (5.9% in the diabetic pediatric group vs. 0.0% in placebo group). The applicant also reports a slight increase in snoring (1.6% incidence in mecasermin-treated Type 1 diabetics vs. 0.0% in placebo-treated Type 1 DM subjects), and one case of sleep apnea reported in a mecasermin-treated Type 2 diabetic; in addition, papilledema was reported in excess in mecasermin-treated subjects relative to placebo (1.9% mecasermin vs. 0.0% in placebo group). Headache and hypoglycemia were clearly reported more frequently in mecasermin-treated patients. A few cases of hypoglycemic seizures were seen exclusively in the mecasermin groups.

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<sup>108</sup> In addition, the submission includes an expert opinion submitted by [ ] that reviews and summarizes the current understanding of the mechanism responsible of the development of proliferative retinopathy; it concludes that the available evidence does not support a risk of retinopathy in association with IGF-I treatment if IGF-I is administered to patients with normal retina, which includes patients with primary IGFD. The principal arguments and conclusions of Dr [ ] analysis are: i) Proliferative retinopathy does not occur without an underlying vascular eye disease – such as occurs in diabetes; ii) the absence of retinopathy in acromegalic patients without diabetes suggests elevated levels of IGF-1 do not cause retinopathy; and iii) the use of mecasermin in patients without underlying retinal ischemia is very unlikely to cause retinopathy.

**Table 2.7.4.2.1.2-1: Adverse Events in Type 1 and Type 2 DM (Adverse Events Associated with Mecasermin in Primary IGFD)<sup>a</sup>**

	Type 1 Diabetes		Type 2 Diabetes		Pediatric Diabetes	
	Active IGF-1	Placebo	Active IGF-1	Placebo	Active IGF-1	Placebo
Total Subjects	376	118	582	148	102	44
Hypoglycemia	310 (82.4%)	91 (77.1)	69 (11.9%)	17 (11.5%)	92 (90.2%)	34 (77.3%)
Hypoglycemic Seizure	1 (0.3%)	0 (0.0%)			1 (1.0%)	0 (0.0%)
Injection Site Hypertrophy	21 (5.6%)	5 (4.2%)			15 (14.7%)	4 (9.1%)
Ear Infection NOS	4 (1.1%)	2 (1.7%)	11 (1.9%)	0 (0.0%)	2 (2.0%)	1 (2.3%)
Otitis Media NOS	7 (1.9%)	0 (0.0%)	4 (0.7%)	0 (0.0%)	6 (5.9%)	0 (0.0%)
Otitis Media Serous NOS	2 (0.5%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Fluid in Middle Ear			2 (0.3%)	0 (0.0%)		
Hypotacusis	1 (0.3%)	0 (0.0%)	4 (0.7%)	0 (0.0%)		
Inner Ear Disorder NOS	1 (0.3%)	0 (0.0%)				
Tympanic Membrane Hyperemia	1 (0.3%)	0 (0.0%)			1 (1.0%)	0 (0.0%)
Tympanic Memb Dis NOS			2 (0.3%)	0 (0.0%)		
Snoring	6 (1.6%)	0 (0.0%)	2(0.3%)	0 (0.0%)		
Sleep Apnea Syndrome			1 (0.2%)	0 (0.0%)		
Papilledema	7 (1.9%)	0 (0.0%)	2 (0.3%)	0 (0.0%)		
Headache	144 (38.3)	38 (32.2%)	170 (29.2%)	39 (26.4%)	54 (52.9%)	26 (59.1%)
Sinus Headache	7 (1.9%)	2 (1.7%)	13(2.2%)	2(1.4%)	1 (1.0%)	0 (0.0%)
Tension Headache	1 (0.3%)	1 (0.8%)	1 (0.2%)	0 (0.0%)		
Migraine NOS	6 (1.6%)	5 (2.5%)	6 (1.0%)	1 (0.7%)	2(2.0%)	0 (0.0%)
Optic Disc Disorder NOS			1 (0.2%)	0 (0.0%)		

<sup>a</sup>Instances where the difference between the incidence of Active and Placebo is > 5% are bolded  
 Source: Appendices 2.7.4.7.1.3, 2.7.4.7.2.3, and 2.7.4.7.3.3

### 7.1.5.6 Additional analyses and explorations

Several “special assessments” were conducted during the mecasermin primary IGFD clinical program to assess somatic, organ-specific growth. Earlier publications and pre-clinical data have suggested that growth of several viscera may outpace linear growth.<sup>109</sup> Assessments of organomegaly included echocardiograms, renal and spleen ultrasounds. In addition, cephalometric radiological evaluations were performed to evaluate excessive mandibular growth (acromegalic features).

### Echocardiograms

<sup>109</sup> Animal data showed, reportedly, increased renal, spleen and cardiac size following mecasermin treatment.

Serial echocardiograms were performed “in select subjects” at baseline and on treatment at 6 to 12 month intervals. The applicant states that 33 subjects (out of 71) had at least two echocardiograms on treatment and groups them “according to the pattern or interpretation of the echocardiographic abnormalities” as follows:

- 3/33 subjects had abnormal echocardiograms at baseline<sup>110</sup>
- 16/33 subjects had echocardiograms which were always normal
- 9/33 had intermittently abnormal echocardiograms but normal afterward<sup>111</sup>
- 5/55 subjects had normal baseline echocardiograms which were reported abnormal subsequently<sup>112</sup>.

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<sup>110</sup> Patent foramen ovale (subject 10-913), patent ductus arteriosus (subject 10-915), and a small ventricular septal defect (18-007); all resolved subsequently while on trial.

<sup>111</sup> The applicant describes the following: small left ventricle (normal echocardiogram one year later) in subject 18-002; a mild cardiac enlargement at 7 years with two subsequent normal echocardiograms (subject 18-004); enlarged right and left ventricle after 18 months of treatment that continued for 2 six-month follow-up evaluations and followed by normal echocardiograms for 7 additional years of treatment (subject 18-006); supranormal left ventricular systolic performance and left atrial dilation seven years into the treatment with subsequent normal echocardiogram on treatment one year later (subject 18-008); mild right ventricular enlargement after approximately 4 years of treatment with two subsequent normal evaluations (10-904); mild pulmonary hypertension following a severe episode of viral bronchitis followed by normal echocardiogram one year later (subject 10-925); intermittent right ventricular enlargement (most recent evaluation 5 years on treatment was normal) (subject 18-010); enlargement of both left and right ventricle after 6 and 12 months of treatment and supranormal left ventricular systolic performance after 2.5 years of treatment (5 subsequent echocardiograms over 4.5 years were normal) (subject 18-013); supranormal left ventricular systolic performance at one evaluation after 7 years of treatment with normal echocardiogram one year later (subject 18-005).

<sup>112</sup> The applicant describes the following: 1) mitral valve prolapse on two evaluations (subject 10-914); 2) enlarged right ventricle approximately 3 years after beginning treatment that was not noted on any follow-up echocardiograms during approximately 10 years of treatment and a small secundum atrial septal defect with left to right shunt first noted after 7 years of mecasermin that was noted on subsequent evaluations through 10 years of treatment with mecasermin (subject 18-003); 3) “slightly large left ventricular systolic performance on annual films for an additional 5 years” noted after 3.5 years of treatment (subject 18-011); 4) “slightly enlarged left and right ventricle after one year of treatment [...] that was generally reported as normal subsequently” and supranormal left ventricular systolic performance which was noted on 2 additional annual evaluations (subject 18-012); 4) tricuspid insufficiency and right atrial and right ventricular enlargement noted after 5 years of treatment (with normal ventricular chamber size, mass and systolic function and without any significant change in cardiac function over the next 5 years)(subject 18-001).

The applicant states that “clinical abnormalities observed on echocardiograms did not result in discontinuation or interruption of mecasermin therapy in any subject.”

This reviewer’s independent analysis of the of the echocardiogram findings follows. It is based primarily on the data presented in Table 16.2.11.6 (entitled “Echocardiographic Reports”) and the information from Dataset “XSPECTST.” A little less than one half of the patients enrolled (33 out of 71) had at least one echocardiographic exam performed.<sup>113</sup> Of these 33 patients, 3 patients had only one echocardiographic exam<sup>114</sup> and 30 patients had more than one exam. Three patients had abnormal echocardiograms at baseline that normalized subsequently.<sup>115</sup> The patients with normal echocardiograms at baseline and subsequent evaluations (N=13) are presented in Table 16. Patients without baseline echocardiograms but with normal initial echocardiograms (i.e. exams performed at a postbaseline timepoint) who had follow-up exams are also presented in Table 16; such patients had their first echocardiogram on trial at times that range between 0.24 years (patient 18005) and 4.54 years (patient 10901). The information displayed in Table 16 indicates that a large proportion of patients had normal echocardiograms at all timepoints. Some had abnormal exams that were noted at various times on treatment and were followed by normal evaluations. A few had abnormalities that appeared to persist; they included mitral valve prolapse in one patient and evidence of ventricular enlargement in a few others (no evidence of worsening was described). Although the lack of a control limits the ability to interpret these results, the general impression is that some patients have occasional evidence of right or left ventricular enlargement and “supranormal left ventricular performance.” It is important to recognize that there were no patient discontinuations due to any of these

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<sup>113</sup> Some echocardiograms were performed locally, others at the two centers involved in the conduct of the trial (CHMCC and UNC).

<sup>114</sup> One patient (10949) had an echocardiogram at baseline and two patients (10918 and 10919) had each an echocardiogram at approximately one year within the trial.

<sup>115</sup> As previously described by the applicant they were patients 10913 (patent foramen ovale), patient 10915 (patent ductus arteriosus), and Patient 18007 (small ventricular septal defect). The three cardiac lesions described above are known congenital cardiac defects that are seen in children and are known to resolve spontaneously.

findings, no description of progression or worsening of these findings, and no associated clinical symptoms described despite the fact that patients continued the treatment long-term. Equally important is the fact that there are no normative cardiac data to compare “historically” these findings in patients with Laron Syndrome.<sup>116</sup> Despite minor discrepancies in the number of patients who had baseline and follow-up ultrasounds, this reviewer’s analysis is, in general, consistent with that of the applicant’s.

**Table 16: Patients with normal baseline or initial echocardiograms (N=27) and follow-up echocardiograms\***

Pt ID	Time of 1 <sup>st</sup> Echo (year)	Time of last Echo (year)	No. of postbaseline echo’s on study	Comments
10909	-0.02	7.73	8	Normal results.
10910	-0.005	2.53	4	Normal results.
10912	-0.002	3.05	3	Normal results.
10914	-0.005	0.96	2	Mitral valve prolapse on both postbaseline echo’s.
10916	-0.032	1.16	2	Normal results.
10917	-0.031	1.16	2	Normal results.
10925	0	3	3	Mild pulmonary hypertension; normal follow-up.
18008	-0.002	8.41	9	The penultimate echo indicated: “supranormal LV systolic performance, LA dilatation, otherwise normal;” subsequent echo: normal result.
18009	-0.008	9.52	9	Normal results.
18010	-0.005	4.88	6	Three echo’s with “large right ventricle; last echo: normal.
18011	-0.01	9.03	10	Ventricular enlargement, supranormal LV function on 7 echos (including last 6). No comments of worsening.
18012	-0.005	9.04	10	Supranormal LV systolic performance (last 3 echo’s) and large LV and RV on two earlier echo’s.
18013	-0.005	8.41	10	Large LV and RV on three early echo’s supranormal LV performance (one echo), last 5 echo’s normal.
10901	4.54	6.57	3	Normal results.
10902	3.86	6.8	4	Normal results.
10903	3.77	6.72	4	Normal results.
10904	3.53	6.60	4	Mild right ventricular enlargement noted on 2 <sup>nd</sup>

<sup>116</sup> Age-matched controls have much larger body sizes and height-matched controls are substantially younger. In addition, cardiomegaly is a well described feature of Laron Syndrome.

				echo, followed by two normal echo's.
10905	3.53	6.60	4	Normal results.
10906	3.50	11.47	9	Normal results.
10907	3.54	6.49	4	Normal results.
10908	3.51	11.07	10	Normal results.
18001	1.09	9.93	11	Tricuspid insufficiency on last 5 echo's.
18002	1.84	6.57	7	On one occasion RV and RA enlargement followed by normal echo.
18003	1.77	6.97	8	RV enlarged on 3 occasions; trivial mitral insufficiency on two exams; small patent foramen ovale/secundum ASD with left to right shunt on 3 exams (including the last one).
18004	1.01	9.09	11	Large RV and "mild cardiac chamber enlargement" one exam each; all other exams including the last two were normal.
18005	0.24	8.5	10	"Supranormal LV systolic performance" on the penultimate exam; normal echo on last exam.
18006	0.97	10.07	12	LV and/or RV enlarged on three exams; last 8 exams were normal.

Source: Table 16.2.11.6 in Study Report 1419 and *Dataset XSPECTST*.

Echo = echocardiogram. LV = left ventricle. RV = right ventricle.

\* Highlighted are comments for those patients who had abnormal echocardiograms at the last evaluation.

## Renal size and function

A subset of 23 patients (16 males and 7 females) was evaluated with serial abdominal ultrasound examinations.<sup>117</sup> Renal length measurements at initial evaluation (baseline or postbaseline) and at the last on-trial measurements are displayed in Table 17. The data are presented as SDscores separately for right and left kidneys. At initial measurements, mean right kidney and mean left kidney SD score were markedly below normal ( $-3.26 \pm 1.54$ , and  $-3.01 \pm 1.71$  respectively); at last measurement they were within the low normal range ( $-1.89 \pm 2.33$  and  $-1.69 \pm 2.47$ ), respectively.<sup>118</sup> The applicant states that "the last available renal length SD scores exceed the upper limit of normal (i.e., were  $>2$ ) in only 2 subjects, 1 of whom (10-901) had a last renal size SD score of  $+2.6$ , and the other of whom (10-907) had a last renal size SD score of  $+2.5$ . [...] No structural abnormalities were observed on ultrasound."

<sup>117</sup> Sixteen of them had baseline information; seven others had initial ultrasounds collected at variable times on treatment (between 0.02 year to approximately 1 year).

<sup>118</sup> The interval between measurements was as short as 1.5 year and as long as 5 years (for most patients was between 3-5 years).

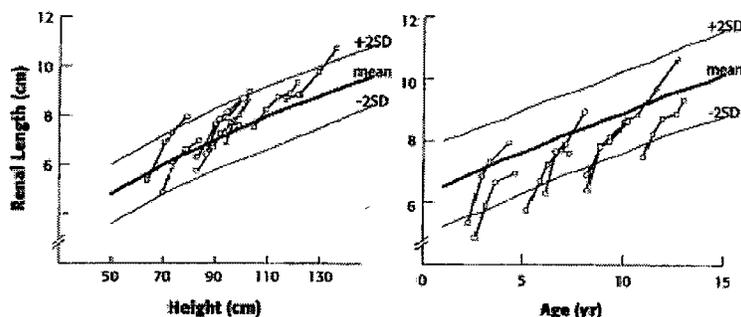
**Table 17: Summary of Renal Lengths Measured by Ultrasound**

Time of Assessment	Right Kidney Length (SD score) N=23	Left Kidney Length (SD score) N=23
Baseline*	-3.26 ± 1.54 (Range -7.47 to -0.28)	-3.01 ± 1.71 (Range -7.07 to 0.17)
Last Measurement	-1.89 ± 2.33 (Range -7.39 to 1.81)	-1.69 ± 2.47 (Range -7.11 to 2.55)

Source: *Dataset XULTRA*

\* For seven patients who did not have baseline measurements the first measurement on trial was used (such measurements ranged between 0.002 and 1.029 years of treatment).

The applicant states that “renal size increased rapidly initially, but slowed in subsequent years” on treatment. Individual graphs for these patients were submitted with the 120-day safety update and showed such profiles. A graphic illustration of these changes for a subgroup of patients from Study F0206s treated with mecasermin for 2 years is provided by applicant’s following figure.



The applicant points out that “there was [...] no evidence of renal dysfunction in any subject while on drug.” Specifically, the mean serum creatinine (± SD) changed minimally (it increased from 0.53 ± 0.1 mg/dL to 0.60 ± 0.14 mg/dL) between the first and the last renal ultrasound examinations over 4.3 ± 1.5 years. Individual glomerulation filtration rates, measured from Technetium-99 scanning were in general consistent with the creatinine observations.<sup>119</sup>

<sup>119</sup> The applicant states that “glomerular filtration rates (GFR) rose in 10/12 subjects followed. There was a slight decrease in GFR for 1 subject (18-013) from 82 to 63 mL/min/1.73m<sup>2</sup> (in the 5 years after the last

## Spleen size

The applicant provides data for 23 patients (16 males and 7 females) and reports that “none of the last spleen measurements for the subjects in this study were above the upper limit of normal on an age-adjusted basis.” Similar to observations made for renal length measurements above, spleen growth “increased rapidly during the first 1-2 years and then slowed.” There were no reports of thrombocytopenia to suggest hypersplenism.

Graphic illustrations of these changes for a subgroup of patients treated with mecasermin long-term in Study F0206s is provided the following figure derived from published data by Backeljau et al (*J Clin Endocrinol Metab* **81**: 3312-3317, 1996). Similar graphic illustrations for individual

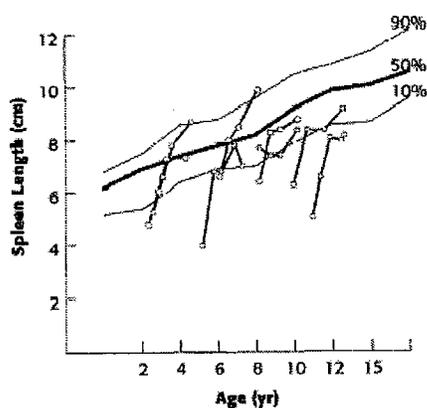


FIG. 4. Change in size of the spleen in eight patients with GHIS during 2 (or 3) yr of treatment with IGF-I. Spleen length was measured by ultrasound. The 10th, 50th, and 90th percentile age standards for spleen length are based on sonographic measurements in normal children reported by Rosenberg *et al.* (40).

patients were submitted with the 120-day safety update and support the above description.

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GFR was obtained, the creatinine clearance rose from 119.5 to 124.3 mL/min/1.73m<sup>2</sup>, and the serum creatinine remained stable at 0.8 mg/dL). One subject (18-008), had a GFR at baseline of 101 mL/min/1.73m<sup>2</sup>, varied between 101 and 237 mL/min/1.73m<sup>2</sup> over the span of 2.5 years on treatment, but had a final GFR of only 45 mL/min/1.73m<sup>2</sup> at the end of 3.5 years of treatment; the creatinine clearance obtained at the same time as the final GFR measurement was normal (101.7 mL/min/1.73m<sup>2</sup>), and remained normal or elevated for the next 5 years.”

## Facial changes

“The applicant states that “change in the appearance of the face described as thickening of the nasal and lip mucosa or coarsening and overgrowth of soft tissue was observed in some subjects and was notably more pronounced at the time of puberty. Following discontinuation of mecasermin, the overgrowth appears to reverse.” Facial changes on treatment, however, were not systematically evaluated.

The applicant provides mandibular cephalometric x-ray data in 8 subjects treated with 80 to 120 µg/kg of mecasermin BID for 6 years. At baseline, facial bones are described as “underdeveloped with small cranial base, small facial dimensions and retrognathic maxilla and mandible.” The applicant indicates that catch-up growth (measured as improvement in standard deviation scores) for several of the facial bones was observed without significant overgrowth of any specific bone. Despite some indication that the mandibular growth was more rapid relative to either the maxilla or anterior or posterior skull bones, there was “no clear evidence of acromegaloid or excessive bony change.” “Significant individual subject variation in facial bone growth” was reported.

### 7.1.6 Less Common Adverse Events

Table 18 lists adverse events occurring with an incidence  $\leq 5\%$  (i.e. in three patients or less) but  $\geq 3\%$  (i.e. in more than two patients) by “preferred term” in order of descending frequency across all organ systems. It summarizes applicant’s Table 16.2.11.3 from Section 5.3.3.2.4. Information on whether the events were deemed “related” by the investigator along with incidence data for such events is also included. The absence of a comparator or background rates makes further interpretation difficult.

Table 18: Adverse events with an incidence  $\leq 5\%$  and  $\geq 3\%$

Adverse event	Number and (%) of patients with event N=71	Number and (%) of patients with event considered related* N=71
Hypoglycemic seizure	3 (4%)	3 (4%)
Hyperglycemia NOS	3 (4%)	2 (3%)
Chest pain	3 (4%)	0 (0%)
Fatigue	3 (4%)	0 (0%)
Hypertrophy NOS	3 (4%)	3 (4%)
Mucosal membrane hyperplasia	3 (4%)	3 (4%)
Pneumonia NOS	3 (4%)	0 (0%)
Adenoidal hypertrophy	3 (4%)	3 (4%)
Mouth breathing	3 (4%)	3 (4%)
Pharyngolaryngeal pain	3 (4%)	0 (0%)
Rhinitis NOS	3 (4%)	0 (0%)
Sleep apnea syndrome	3 (4%)	3 (4%)
Hyperkeratosis follicularis and parafollicularis	3 (4%)	0 (0%)
Echocardiogram [ab]normal	3 (4%)	3 (4%)
Flank pain	3 (4%)	1 (1%)
Anemia NOS	3 (4%)	0 (0%)
Iron deficiency anemia	3 (4%)	0 (0%)
Lacrimation increased	3 (4%)	0 (0%)
Tachycardia NOS	3 (4%)	2 (3%)
Ventricular hypertrophy	3 (4%)	3 (4%)
Body fat disorder	2 (3%)	0 (0%)
Injection site pain	2 (3%)	2 (3%)
Febrile infection	2 (3%)	1 (1%)
Fungal infection NOS	2 (3%)	0 (0%)
Molluscum contagiosum	2 (3%)	0 (0%)
Mumps	2 (3%)	0 (0%)
Otitis externa NOS	2 (3%)	1 (1%)
Pharyngitis streptococcal	2 (3%)	0 (0%)
Dyspnea	2 (3%)	1 (1%)

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Nasal disorder NOS	2 ( 3%)	0 ( 0%)
Wheezing	2 ( 3%)	0 ( 0%)
Nausea	2 ( 3%)	0 ( 0%)
Retching	2 ( 3%)	1 (1%)
Tooth disorder NOS	2 ( 3%)	0 ( 0%)
Toothache	2 ( 3%)	0 ( 0%)
Middle ear disorder NOS	2 ( 3%)	1 ( 1%)
Alanine aminotransferase increased	2 ( 3%)	1 (1%)
Aspartate aminotransferase increased	2 ( 3%)	1 (1%)
Blood cholesterol increased	2 ( 3%)	0 ( 0%)
Blood glucose increased	2 ( 3%)	0 ( 0%)
Limb discomfort NOS	2 ( 3%)	0 ( 0%)
Myalgia	2 ( 3%)	2 ( 3%)
Acanthosis nigricans	2 ( 3%)	0 ( 0%)
Acrochordons	2 ( 3%)	1 ( 1%)
Contusion	2 ( 3%)	0 ( 0%)
Skin hyperpigmentation	2 ( 3%)	0 ( 0%)
Skin hypertrophy	2 ( 3%)	2 ( 3%)
Sweating increased	2 ( 3%)	0 ( 0%)
Eye redness	2 ( 3%)	0 ( 0%)
Papilledema	2 ( 3%)	2 ( 3%)
Strabismus	2 ( 3%)	0 (%)
Visual acuity reduced	2 ( 3%)	1 ( 1%)
Adenoidectomy	2 ( 3%)	2 ( 3%)
Tibia fracture	2 ( 3%)	0(0%)
Cardiomegaly NOS	2 ( 3%)	2 ( 3%)
Congenital atrial septal defect	2 ( 3%)	0 (%)
Criptorchidism	2 ( 3%)	0 (%)
Pigmented nevus	2 ( 3%)	1 (1%)
Abnormal behavior NOS	2 ( 3%)	1 (1%)
Emotional disturbance NOS	2 ( 3%)	0 (0%)
Nervousness	2 ( 3%)	2 ( 3%)
Sleep terror	2 ( 3%)	2 ( 3%)
Dysuria	2 ( 3%)	0 (0%)

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Nephrolithiasis	2 ( 3%)	1 (1%)
Pollakiuria	2 ( 3%)	0 (0%)

\*Includes all events reported as “possible”, “probable” or missing relationship to the study medication.

Source: Table 16.2.11.3

**Table 2.7.4.2.1.2-3: Adverse Events Not Commonly Associated with Mecasermin Use in Primary IGFD\***

	Type 1 Diabetes		Type 2 Diabetes		Pediatric Diabetes	
	Active IGF-1	Placebo	Active IGF-1	Placebo	Active IGF-1	Placebo
<b>Total Subjects</b>	<b>376</b>	<b>118</b>	<b>582</b>	<b>148</b>	<b>102</b>	<b>44</b>
Hyperglycemia NOS	44 (11.7%)	2 (1.7%)	30 (5.2%)	9(6.1%)	4 (3.9%)	1 (2.3%)
Dizziness	28 (7.4%)	2 (1.7%)	74 (12.7%)	14 (9.5%)	2 (2.0%)	1 (2.3%)
Edema Peripheral	37 (9.8%)	4 (3.4%)	102 (17.5%)	12 (8.1%)	5 (4.9%)	0 (0.0%)
Arthralgia	43 (11.4%)	7 (5.9%)	102 (17.5%)	27 (18.2%)	6 (5.9%)	1 (2.3%)
Pain in Jaw	41 (10.9%)	1 (0.8%)	102 (17.5%)	10 (6.8%)	6 (5.9%)	0 (0.0%)
Back Pain	24 (6.4%)	1 (0.8%)	80 (13.7%)	12 (8.1%)	3 (2.9%)	1 (2.3%)
Nausea	35 (9.3%)	16 (13.6%)	48 (8.2%)	7 (4.7%)	4 (3.9%)	8 (18.2%)
Abdominal Pain Upper	19 (5.1%)	8 (6.8%)	17 (2.9%)	13(2.0%)	12 (11.8%)	8 (18.2%)
Abdominal Pain NOS	11 (2.9%)	6 (5.1%)	19 (3.3%)	2(1.4%)	5 (4.9%)	5 (11.4%)
Nasopharyngitis	52 (13.8%)	13 (11.0%)	61(10.5%)	14 (9.5%)	27 (26.5%)	6 (13.6%)
Pharyngolaryngeal Pain	22 (5.9%)	19 (16.1%)	27 (4.6%)	4 (2.7%)	13 (12.7%)	16 (36.4%)

\*Instances where the difference between the incidence of Active and Placebo is > 5% are bolded

Source: Appendices 2.7.4.7.1.3, 2.7.4.7.2.3, and 2.7.4.7.3.3

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The applicant presents a tabulation of adverse events from the Type 1 and Type 2 diabetes studies of mecasermin (adult and pediatric) that “were not commonly associated with mecasermin in patients with primary IGFD.” Overall, adverse events for which the incidence was 5% or higher in mecasermin-treated diabetic subjects relative to placebo-treated subjects included hyperglycemia, dizziness, peripheral edema, arthralgia, jaw pain, back pain and nasopharyngitis. Adverse events that were higher in the IGF-I pediatric cohort relative to the placebo pediatric cohort were hyperglycemia, edema peripheral, arthralgia, pain in the jaw, back pain, and nasopharyngitis.

## 7.1.7 Laboratory Findings

### 7.1.7.1 Overview of laboratory testing in the development program

Laboratory data were obtained in a subset of patients. Twenty-three subjects (out of 71 enrolled) had routine serial laboratory evaluations; 16 more had sporadic laboratory

evaluations. The applicant's analyses of laboratory values are, in general limited to the 23 subjects with serial measurements available. The analysis of various analytes was performed at several laboratories.<sup>120</sup> The laboratory measurements collected during the clinical trials included standard hematology, serum chemistries, thyroid function tests, plasma or serum IGF-1 and anti-IGF-1 antibodies (in studies F0206s, F0375g, F0632g and F0671g). This reviewer has conducted independent analyses using information presented in the Dataset XLAB. In general, they are in agreement with the applicant's analysis.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

As the mecasermin clinical program in primary IGFD includes almost exclusively non-controlled clinical data and background rates of abnormal laboratory findings for the population studied are not available, the laboratory results cannot be presented in a comparative way. Consequently, this review follows largely along the lines of the applicant's submission, which presents a descriptive analysis of the laboratory results.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### 7.1.7.3.1 *Analyses focused on measures of central tendency*

Descriptions of mean values for all analytes at the beginning and end of mecasermin treatment were submitted in the 120-day safety update and are summarized in Table #19. The table incorporates data for 7 out of 12 years due to the relatively small size of the dataset for years 8-12. Overall, there were no clinically meaningful changes in mean values for the chemistry and hematology analytes presented, which is summarized in this section. The mean hemoglobin concentration increased substantially during the study but this is due to the fact that at baseline as many as 36.4% of patients had anemia which was corrected during the clinical

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<sup>120</sup> Laboratory samples for safety assessments for F0206s were analyzed by University of North Carolina, (Chapel Hill, NC). Laboratory samples for safety assessments for Studies F0375g, F0632g, and F0671g were shipped to and analyzed by [redacted]. Laboratory samples for Study 1419 were analyzed by the clinical laboratories at University of North Carolina (UNC) and Children's Hospital Medical Center, Cincinnati, OH (CHMCC). Samples for IGF-1 at baseline were analyzed in a number of assays. Anti-IGF-1 antibodies were analyzed at Genentech, Inc. (South San Francisco, CA) for studies F0206s, F0375g, F0632g, and F0671g during treatment.

trial. Cholesterol and triglyceride concentrations, already abnormally high at baseline, appeared to increase under treatment.<sup>121</sup>

**Table19: Mean Values for Analytes Evaluated in Study 1419**

Analyte	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
<b>Hemoglobin (g/dL)</b>								
N	33	32	30	26	23	18	16	17
Mean	12.0	12.0	12.5	12.9	12.9	13.2	13.3	13.4
(SD)	(0.9)	(1.2)	(1.4)	(1.2)	(0.8)	(0.8)	(0.9)	(0.9)
Median	12.0	12.2	12.7	12.8	12.8	13.4	13.3	13.3
Minimum	10.3	8.8	10.1	10.5	11.2	11.1	11.8	12.0
Maximum	13.9	14.5	15.6	15.2	15.1	14.4	15.3	15.0
N	NA	27	26	22	22	18	16	16
Change*		0.0	0.5	0.9	1.0	1.4	1.5	1.5
(SD)		(1.0)	(1.2)	(1.1)	(0.9)	(1.0)	(1.1)	(1.0)
<b>Platelets (x10<sup>9</sup>/L)</b>								
N	28	29	29	26	23	17	16	17
Mean	336.4	323.0	281.7	274.8	272.3	245.4	261.5	278.4
(SD)	(90.2)	(58.1)	(75.5)	(42.9)	(56.0)	(44.1)	(60.6)	(67.2)
Median	318.5	313.0	285.0	278.0	263.0	247.0	256.0	263.0
Minimum	177.0	185.0	112.0	207.0	212.0	179.0	189.0	175.0
Maximum	538.0	496.0	473.0	359.0	453.0	341.0	416.0	441.0
N	NA	23	24	20	19	16	15	16
Change*		-20.2	-70.1	-85.7	-71.6	-97.7	-86.0	-64.8
(SD)		(69.7)	(97.6)	(78.2)	(74.0)	(90.9)	(100.2)	(84.9)
<b>White Blood Count (x10<sup>9</sup>/L)</b>								
N	29	31	30	26	21	18	16	17
Mean	9.0	9.4	8.4	9.3	7.9	8.4	8.7	8.2
(SD)	(3.6)	(3.5)	(2.6)	(2.8)	(1.8)	(3.0)	(3.2)	(2.9)
Median	8.8	9.2	7.7	9.3	7.4	7.5	8.1	8.2
Minimum	3.7	4.1	4.7	3.6	(4.8)	(4.9)	5.0	4.1
Maximum	16.4	18.3	13.7	15.4	11.4	15.4	17.6	17.3
N	NA	25	25	20	20	18	16	16
Change*		0.2	-1.1	-0.8	-0.5	-0.5	-0.3	-0.7
(SD)		(3.6)	(3.5)	(3.0)	(2.6)	(2.8)	(3.8)	(3.3)
<b>Eosinophils (%)</b>								
N	23	29	27	23	21	17	16	16
Mean	5.1	3.5	3.8	3.6	3.4	4.1	4.0	4.1
(SD)	(5.2)	(3.5)	(3.0)	(2.3)	(3.6)	(3.2)	(2.3)	(2.6)
Median	2.6	3.0	3.8	3.8	2.0	4.0	4.0	3.0
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0
Maximum	20.0	17.8	12.1	8.8	14.0	13.0	9.0	8.7
N	NA	19	18	17	14	10	9	10

<sup>121</sup> The mean (± SD) cholesterol serum concentrations increased slightly during mecasermin from 170.0 ± 36.5 mg/dL, to 187.0 ± 37.1 mg/dL. This observation was consistent with the one reported by Laron and Klinger in Hormone Research 1993; 40 (1-3): 16-22. In this study of 13 patients with primary IGFD the mean (±SEM) baseline serum cholesterol level was 175.7 ± 13.2 mg/dL, and increased to a mean of 191.6 ± 11.3 mg/dL after 12 months of mecasermin treatment. The mean (± SD) triglycerides increased from 78.1 ± 36.6 mg/dL, to 143.7 ± 103.5 mg/dL.

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Change* (SD)		-1.5 (6.4)	-0.7 (4.9)	-1.8 (5.0)	-0.6 (4.4)	-0.7 (3.0)	-1.8 (5.5)	-0.8 (4.8)
<b>Total Bilirubin (mg/dL)</b>								
N	21	23	23	18	19	17	14	11
Mean (SD)	0.5 (0.2)	0.5 (0.1)	0.5 (0.2)	0.6 (0.3)	0.6 (0.1)	0.5 (0.2)	0.4 (0.1)	0.4 (0.2)
Median	0.5	0.4	0.5	0.6	0.6	0.4	0.4	0.4
Minimum	0.2	(0.2)	0.3	0.3	0.	0.1	0.2	0.1
Maximum	0.8	0.8	0.9	1.6	0.7	1.0	0.6	0.7
N	NA	21	21	15	17	15	12	10
Change* (SD)		-0.0 (0.2)	0.0 (0.2)	0.1 (0.2)	0.1 (0.2)	-0.0 (0.2)	-0.1 (0.2)	-0.1 (0.2)
<b>ALT (IU/L)</b>								
N	24	28	27	23	20	17	15	16
Mean (SD)	18.5 (7.9)	19.0 (7.5)	19.3 (8.9)	24.0 (17.2)	23.8 (23.6)	43.0 (73.0)	25.3 (16.7)	23.3 (16.9)
Median	15.0	18.0	17.0	19.0	14.0	16.0	19.0	18.5
Minimum	8.0	9.0	6.0	9.0	8.0	9.0	10.0	7.0
Maximum	36.0	36.0	44.0	78.0	98.0	265.0	75.0	-76.0
N	NA	21	21	17	17	15	13	14
Change* (SD)		-0.1 (6.4)	-0.0 (9.6)	7.4 (17.5)	5.0 (24.3)	26.9 (75.0)	5.5 (17.0)	6.0 (14.5)
<b>AST(IU/L)</b>								
N	27	27	26	21	21	18	15	17
Mean (SD)	44.1 (12.0)	37.7 (12.6)	35.8 (9.3)	39.3 (18.2)	37.2 (21.3)	44.1 (31.3)	37.1 (24.8)	34.8 (11.4)
Median	44.0	35.0	35.0	33.0	29.0	33.5	29.0	34.0
Minimum	19.8	20.0	21.0	17.0	18.0	18.0	16.0	18.0
Maximum	74.0	72.0	68.0	87.0	90.0	120.0	97.0	57.0
N	NA	24	24	19	19	16	13	15
Change* (SD)		-5.9 (11.8)	-9.5 (10.3)	-5.8 (19.8)	-8.4 (24.0)	0.3 (31.9)	-8.3 (20.4)	-9.8 (13.8)
<b>LDH (IU/L)</b>								
N	22	22	22	17	18	11	8	1
Mean (SD)	290.0 (67.6)	331.0 (268.6)	253.3 (50.2)	285.8 (171.4)	221.7 (47.2)	221.3 (43.6)	185.4 (19.6)	222.0
Median	278.0	248.0	245.5	228.0	212.5	225.0	180.5	222.0
Minimum	197.0	165.0	169.0	169.0	157.0	171.0	161.0	
Maximum	397.0	1411	391.0	794.0	336.0	310.0	226.0	
N	NA	20	20	15	16	9	6	0
Change* (SD)		52.4 (257.3)	-28.1 (65.1)	-3.5 (196.1)	-66.9 (76.8)	-47.9 (55.8)	-55.3 (27.5)	
<b>Creatinine (mg/dL)</b>								
N	33	34	31	26	23	18	16	17
Mean (SD)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.5 (0.1)	0.5 (0.1)
Median	0.5	0.5	0.5	0.6	0.6	0.6	0.5	0.5
Minimum	0.3	0.2	0.3	0.2	0.3	0.3	0.3	0.3
Maximum	0.8	0.7	0.8	-0.8	0.9	0.8	0.7	-0.8
N	NA	29	29	24	23	18	16	17
Change* (SD)		-0.1 (0.1)	-0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	-0.0 (0.1)	-0.1 (0.1)	-0.0 (0.1)

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<b>Creatinine Clearance (ml/min/1.73 m2)</b>								
N	33	34	31	26	23	18	16	16
Mean	95.5	119.0	112.8	117.8	116.6	117.7	143.3	144.9
(SD)	(30.7)	(37.6)	(26.2)	(46.9)	(31.9)	(26.8)	(34.8)	(40.2)
Median	89.4	108.8	109.1	116.5	119.4	115.9	131.9	145.6
Minimum	53.5	55.8	55.4	59.0	65.8	76.2	107.6	69.7
Maximum	176.0	237.6	174.0	279.1	165.5	175.8	233.4	242.4
N	NA	29	29	24	23	18	16	16
Change*		21.5	19.3	17.8	27.5	36.8	62.7	61.6
(SD)		(21.3)	(26.8)	(33.7)	(29.5)	(25.2)	(29.7)	(31.5)
<b>BUN (mg/dL)</b>								
N	33	33	31	26	23	18	16	17
Mean	18.0	13.2	14.6	14.5	14.1	13.5	13.6	13.6
(SD)	(6.1)	(6.6)	(5.1)	(6.5)	(6.6)	(4.8)	(6.6)	(5.4)
Median	17.0	12.0	13.0	13.3	12.0	13.0	11.0	12.0
Minimum	9.0	3.3	9.0	6.0	8.0	5.0	8.0	8.0
Maximum	35.0	34.0	26.0	33.0	32.0	25.0	30.0	28.0
N	NA	28	29	24	23	18	16	17
Change*		-4.2	-3.2	-3.7	-4.5	-4.0	-4.2	-2.4
(SD)		(5.0)	(4.5)	(6.4)	(4.3)	(6.0)	(6.6)	(6.0)
<b>Sodium (meq/L)</b>								
N	33	33	30	24	22	18	16	12
Mean	138.2	138.4	139.1	139.3	139.7	140.3	140.1	139.8
(SD)	(2.8)	(2.7)	(2.1)	(2.5)	(2.5)	(2.3)	(2.5)	(2.3)
Median	138.0	139.0	139.0	139.0	140.0	140.0	139.5	140.0
Minimum	132.0	130.0	136.0	135.0	132.0	136.0	137.0	137.0
Maximum	144.0	143.0	145.0	145.0	145.0	146.0	144.0	143.0
N	NA	28	28	22	22	18	16	12
Change*		-0.1	1.0	1.5	1.8	1.6	1.3	0.7
(SD)		(3.6)	(3.3)	(4.1)	(3.4)	(3.4)	(3.4)	(3.3)
<b>Chloride (meq/L)</b>								
N	28	25	26	19	20	18	16	12
Mean	105.8	106.5	106.0	105.3	106.2	105.6	106.6	102.8
(SD)	(3.1)	(3.3)	(3.0)	(2.8)	(2.0)	(2.3)	(2.0)	(2.9)
Median	105.0	107.0	106.0	105.0	106.5	105.0	106.0	103.5
Minimum	99.0	99.0	101.0	100.0	102.0	103.0	104.0	98.0
Maximum	112.0	112.0	111.0	110.0	111.0	110.0	110.0	107.0
N	NA	24	25	18	19	17	15	11
Change*		1.0	0.4	0.0	1.0	-0.2	0.7	-3.8
(SD)		(4.0)	(4.3)	(3.7)	(3.3)	(4.1)	(3.6)	(4.3)
<b>CO2 (meq/L)</b>								
N	13	10	12	6	5	7	8	11
Mean	20.6	20.5	22.4	22.8	22.8	23.7	23.4	25.1
(SD)	(2.5)	(3.4)	(3.3)	(2.6)	(1.9)	(1.1)	(3.7)	(2.3)
Median	21.0	20.0	22.5	22.5	23.0	23.0	24.0	25.0
Minimum	17.0	15.0	18.0	19.0	20.0	23.0	15.0	21.0
Maximum	26.0	25.0	27.0	27.0	25.0	26.0	27.0	28.0
N	NA	9	10	5	1	0	0	0
Change*		0.6	1.5	3.0	3.0	NA	NA	NA
(SD)		(3.1)	(3.6)	(2.8)				
<b>Potassium (meq/L)</b>								
N	33	33	31	24	22	18	16	12

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Mean	4.6	4.9	4.8	4.6	4.7	4.5	4.4	4.1
(SD)	(0.5)	(0.8)	(0.5)	(0.9)	(0.4)	(0.4)	(0.4)	(0.3)
Median	4.6	4.7	4.8	4.5	4.6	4.5	4.3	4.1
Minimum	3.9	3.8	4.0	3.8	4.0	3.7	3.7	3.4
Maximum	6.2	8.0	6.0	8.4	5.5	5.2	5.3	4.7
N	NA	28	29	22	22	18	16	12
Change*		0.2 (0.9)	0.2 (0.6)	0.0 (1.2)	-0.0 (0.7)	-0.3 (0.6)	-0.4 (0.7)	-0.8 (0.6)
(SD)								
<b>Calcium (mg/dL)</b>								
N	29	29	29	24	20	17	14	17
Mean	9.4	9.5	9.5	9.5	9.5	9.6	9.4	9.4
(SD)	(0.3)	(0.6)	(0.4)	(0.4)	(0.4)	(0.3)	(0.3)	(0.3)
Median	9.3	9.4	9.5	9.5	9.5	9.4	9.4	9.4
Minimum	8.8	8.4	8.6	8.9	8.7	8.9	8.8	8.6
Maximum	10.2	11.0	10.7	10.3	10.3	10.1	10.0	9.9
N	NA	25	26	21	19	16	13	16
Change*		0.1	0.1	0.1	0.2	0.3	0.1	0.0
(SD)		(0.7)	(0.4)	(0.4)	(0.4)	(0.4)	(0.3)	(0.4)
<b>PO4 (mg/dL)</b>								
N	24	26	27	24	21	17	14	17
Mean	4.4	4.6	5.0	4.7	4.7	4.6	4.6	4.4
(SD)	(0.8)	(0.8)	(0.6)	(0.7)	(0.5)	(0.9)	(0.9)	(0.8)
Median	4.6	4.9	5.0	4.8	4.8	4.9	4.7	4.6
Minimum	2.8	2.2	3.5	3.3	3.5	2.6	3.1	3.0
Maximum	5.8	5.7	5.9	6.4	5.4	6.0	5.9	5.8
N	NA	18	20	19	14	10	7	12
Change*		0.4	0.6	0.4	0.3	0.2	0.2	0.3
(SD)		(0.9)	(1.1)	(1.1)	(0.9)	(0.9)	(0.8)	(0.9)
<b>Glucose (mg/dL)</b>								
N	36	34	34	25	20	17	13	12
Mean	71.0	82.2	88.7	92.4	88.0	88.0	87.1	87.3
(SD)	(15.4)	(19.9)	(42.3)	(27.5)	(15.7)	(14.1)	(16.0)	(9.1)
Median	70.0	79.7	82.5	89.0	89.5	89.0	90.0	84.5
Minimum	43.0	51.0	46.0	49.0	50.0	63.0	45.0	76.0
Maximum	109.0	152.0	297.0	176.0	114.0	122.0	106.0	103.0
N	NA	31	32	22	20	17	13	12
Change*		13.6	17.2	25.7	21.3	23.0	20.7	20.3
(SD)		(23.2)	(43.1)	(32.8)	(15.7)	(19.0)	(14.2)	(12.7)
<b>Cholesterol (mg/dL)</b>								
N	34	33	31	23	24	17	13	17
Mean	170.0	183.4	184.3	177.6	188.2	190.8	179.7	187.0
(SD)	(36.5)	(51.8)	(43.2)	(26.0)	(39.6)	(44.0)	(38.1)	(37.1)
Median	170.1	180.0	189.0	177.0	189.0	185.0	177.0	194.0
Minimum	104.0	108.0	88.0	128.0	129.0	129.0	131.0	122.0
Maximum	249.0	336.0	286.0	216.0	263.0	273.0	241.0	277.0
N	NA	31	30	21	22	16	12	16
Change*		12.5	14.3	13.8	22.9	28.6	19.8	27.2
(SD)		(43.6)	(28.7)	(18.4)	(39.9)	(46.0)	(49.2)	(43.3)
<b>Triglycerides (mg/dL)</b>								
N	34	30	29	21	22	17	13	12

Mean	78.1	84.3	90.0	104.5	101.5	109.9	83.8	143.7
(SD)	(36.6)	(39.2)	(35.0)	(51.7)	(70.6)	(64.1)	(29.1)	(105.3)
Median	68.5	75.5	86.0	93.0	80.5	88.0	79.0	111.0
Minimum	26.6	37.0	37.0	44.0	43.0	41.0	39.0	50.0
Maximum	183.0	179.0	190.0	286.0	364.0	304.0	150.0	430.0
N	28	28	19	20	16	12	11	11
Change*	14.1	13.7	31.1	24.8	41.3	18.3	79.5	81.5
(SD)	(39.2)	(24.8)	(64.0)	(42.1)	(61.5)	(41.1)	(104.6)	(65.0)
<b>Uric Acid (mg/dL)</b>								
N	23	24	23	18	18	11	8	1
Mean	3.5	3.2	3.1	3.3	3.0	2.9	2.6	3.9
(SD)	(0.9)	(0.9)	0.9	1.1	(0.7)	(0.8)	(0.9)	3.9
Median	3.4	3.1	3.2	3.2	3.0	3.0	2.6	
Minimum	2.0	1.8	1.7	1.7	1.8	1.7	1.7	
Maximum	4.9	5.0	4.8	5.6	4.6	4.6	4.1	
N	NA	21	20	15	16	9	6	0
Change*		-0.3	-0.4	-0.4	-0.5	-0.9	-1.3	NA
(SD)		(0.8)	(0.9)	(1.4)	(1.1)	(0.9)	(1.1)	
<b>Alkaline Phosphatase (IU/L)</b>								
N	29	28	28	23	20	18	14	17
Mean	160.1	225.1	201.5	203.7	189.4	181.9	174.9	174.1
(SD)	(42.5)	(151.7)	(51.9)	(52.3)	(51.8)	(49.3)	(37.8)	(38.2)
Median	162.0	196.0	206.0	198.0	186.5	176.5	165.5	162.0
Minimum	86.0	105.0	107.0	82.0	14.0	93.0	122.0	108.0
Maximum	252.0	959.0	310.0	308.0	280.0	254.0	256.0	250.0
N	NA	24	24	19	18	16	12	15
Change*		75.0	42.6	43.1	43.1	39.2	29.2	25.6
(SD)		(162.5)	(48.3)	(41.2)	(47.5)	(40.0)	(25.1)	(38.6)

N= number of patients with variable.

\* Mean change from baseline

Source: 120-day Safety Update.

There were no changes in urine specific gravity over 7 years of treatment. Visual inspection of the urinalysis results did not identify any evidence of proteinuria or hematuria.

#### 7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

In analyzing laboratory results that represent shifts above or below the normal range it is important to recognize that a large proportion of the patients enrolled had abnormal baseline laboratory values. Applicant's Table (below) summarizes the number of patients with baseline laboratory values reported as low or high at baseline for the specific analytes.<sup>122</sup> AST and LDH had the highest percentage of laboratory abnormalities at baseline (56% and 55%, respectively). For the 15 subjects with elevated baseline ASTs, the mean AST value was 44.1 IU/L (range: 19.8 to 74 IU/L). For the 12 patients who had LDH elevations at baseline; the values ranged from 197 to 397 IU/L; in 9 of 12 subjects there was a concomitant mild elevation in AST. The elevations in AST and LDH were described as "minimal" and "co-existing at

<sup>122</sup> For this Table baseline value was defined as the values closest to the time of the first administered rhIGF-I dose.

baseline.” The BUN elevations were mild and were accompanied by normal creatinine concentrations. Twelve out of 33 subjects had a low baseline hemoglobin. The applicant states that “in all but one subject, the anemia improved during rhIGF-1 treatment.” It is important to recognize that many of the patients enrolled were from developing countries where nutritional deficiencies and intestinal parasites are more prevalent (many of the enrolled patients had treatment for intestinal parasites and received iron/multivitamins.<sup>123</sup>

Analyte	Number Low/Total (%)	Number Elevated/Total (%)
<b>Chemistries</b>		
AST (SGOT)	-----	15/27 (56)
ALT (SGPT)	-----	0/24 (0)
Blood urea nitrogen (BUN)	-----	10/33 (30)
Cholesterol	-----	12/34 (35)
Triglycerides	-----	4/34 (12)
L.DH	-----	12/22 (55)
<b>Hematology</b>		
Eosinophils (%)	-----	8/23 (35)
Hematocrit	9/27 (33)	-----
Hemoglobin	12/33 (36)	-----
Platelets	-----	5/28 (18)

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## A. Hematology

### Hemoglobin

Several subjects had low hemoglobin levels at baseline and at various times during the clinical trial.<sup>124</sup> The applicant states that

<sup>123</sup> Intestinal parasite infestations were documented in 4 subjects. Eight (35%) of patients had elevated eosinophil counts at baseline. Twelve subjects had one or more recurrences of eosinophil counts >5%.

<sup>124</sup> 12/33 (36.4%) patients had low hemoglobin at baseline, 15/32 (46.9%) at Year 1, 12/30 (40.0%) at Year 2, 2/26 (7.7%) at Year 3, 1/23 (4.3%) at Year 4, 2/18 (11.1%) at Year 5, 1/16 (6.3%) at Year 6, 0/17 (0%) at Year 7, 0/12 (0%) at Year 8, 1/12 (10%) at Year 9, 0/13 (0%) at Year 9, 0/13 (0%) at Year 10, 0/15 (0%) at Year 11 and 0/14 (0%) at Year 12.

Anemia characterized by hemoglobin and/or hematocrit below age-adjusted lower limit of normal was seen prior to treatment with mecasermin in 18 of 23 subjects evaluated. The anemia resolved in most subjects during the course of mecasermin therapy.

This reviewer adds the following observations:

None of the baseline hemoglobin concentrations were below 10 mg/dL.<sup>125</sup> Of the 332 hemoglobin values collected on mecasermin treatment, several were below 10 mg/dL. None were < 8.8 g/dL. All these measurements were accompanied by values that later were within or close to the normal range for age. Above-normal Hb levels were reported by 5 patients. Most observations were either isolated findings, or were non-progressive elevations.

### **Platelets**

There were no abnormally low platelet counts at baseline. During the course of the clinical trial there was only one platelet count flagged as “low” (at Year 2). A few patients had platelet counts above the upper limit of normal at baseline and beyond.<sup>126</sup> The applicant states that

Platelet levels exceeded normal levels prior to treatment in 5 subjects but normalized during mecasermin therapy. In other subjects, the platelet counts were within the high normal range and fell closer to the mean for age as mecasermin therapy progressed. The cause(s) for the observation concerning platelets is not known.

This reviewer adds the following observations:

Most of the baseline measurements were within normal limits; none was low and several platelet elevations of no clinical relevance were observed.<sup>127</sup> On trial there were 364 platelet counts performed in 33 subjects but no cases of clinically relevant platelet count reduction were observed. The lowest platelet measurement on trial was 88,000 in patient 10909, an isolated

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<sup>125</sup> Twenty-eight patients had hemoglobin concentrations measured prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided. Hemoglobin measurements and measurements for all other analytes collected during the 6-month placebo phase of Study F0375g were all reported as “negative” timepoints with respect to the time of mecasermin treatment initiation.

<sup>126</sup> 5/28 (17.9%) patients had high platelet counts at baseline, 3/29 (10.3%) at Year 1, 2/29 at Year 2, and 1/23 (4.3%) at Year 4; no other above-abnormal measurements were recorded at any other timepoints through Year 12.

<sup>127</sup> Twenty-six patients had platelet counts measured prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

finding at 1.5 years of therapy, preceded and followed by multiple normal measurements. No significant platelet elevations were noted.

## **Eosinophils**

Several patients had increased eosinophil counts at baseline and at various times during the clinical trial.<sup>128</sup> The applicant states that

Eosinophilia was noted during the study in 18 of 23 children. Most often these elevations were mild but were markedly elevated in subjects with frequent infections and/or confirmed intestinal parasites.

Reviewer's observations:

Most of the baseline eosinophil counts were normal and several were reported as "low;" fourteen measurements (in 8 patients) were high (range 3.05 to 20%; 50 % of them were above 10%).<sup>129</sup> Twenty-nine patients had 304 eosinophil counts on mecasermin during the trial; of these, 65 eosinophil counts in 19 patients were above upper limit of normal (range of values: 3.68 % to 17.8%; 16 patients had eosinophil counts > 10%).<sup>130</sup>

## **B. Liver function tests**

### **LDH**

Several subjects had elevated LDH levels at baseline and during the clinical trial.<sup>131</sup>

Applicant's presentation of LDH results is summarized as follows:

- 16 of 21 subjects (76 %) had elevated LDH measurements prior to initiation of mecasermin; in six of these, LDH "remained abnormal during the first two to four

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<sup>128</sup> 8/23 (34%) at baseline, 3/29 (10%) at Year 1, 7/27 (25%) at Year 2, 5/23 (21%) at Year 3, 4/21 (19%) at Year 4, 5/17 (24%) at Year 5, 6/16 (37%) at Year 6, 7/16 (43%) at Year 7, 4/11 (36%) at Year 8, 2/10 (20%) at Year 9, 0/6 (0%) at Year 10, 3/4 (75%) at Year 11, and 1/3 (33%) at Year 12.

<sup>129</sup> Twenty patients had eosinophil counts measured prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

<sup>130</sup> Patients 10906 and 18005 had 10 such counts, patient 18008 had such counts; patients 10902, 10910, and 18007 had 3 counts; patient 1901 had 4 counts, patients 10903, 10907, 10912, 18001, 18003, 18009, 18012, and 18013 had 2 such counts and patients 10904, 10914, 18004 and 18006 had only one elevated eosinophil count.

<sup>131</sup> 12/22 (54%) at baseline, 15/22 (68%) at Year 1, 14/22 (63%) at Year 2, 7/17 (41%) at Year 3, 4/18 (22%) at Year 4, 3/11 (27%) at Year 5, 0/8 (0%) at Year 6, and 0/1 (0%) at Years 7 and 11 respectively (no measurements were available for Years 8 through 10).

years of therapy and then normalized;” in six other subjects LDH levels remained “above the normal for age and sex at most follow-up visits.”

- nine subjects had normal LDH at baseline and above normal levels subsequently; five of them had only sporadic elevations

This reviewer’s analysis adds the following observations:

At baseline, twelve patients had LDH elevations in the abnormal range but none was higher than 1.5X ULN.<sup>132</sup> During the trial, 219 above-normal LDH elevations were recorded in twenty-three patients.<sup>133</sup> There were only 4 elevations  $\geq$  2X ULN: 18003 (3.1X ULN), 18006 (2.6X ULN), 18008 (2.9 ULN), and 18010 (2.6X ULN).

## AST

Several subjects had elevated AST levels at baseline and at various timepoints during the clinical trial.<sup>134</sup> Applicant’s presentation of AST results is summarized as follows:

- 14 of 23 subjects (61 %) had AST elevation prior to treatment; in 13 of them, “AST was mildly elevated at two or more subsequent visits during treatment.”
- two subjects with normal AST prior to mecasermin treatment (patients 18-010 and 10-908) “had subsequent mild elevation of AST on two occasions each with normal ALT during 5 years and 11.1 years of mecasermin treatment respectively.”

This reviewer adds the following observations:

At baseline, fifteen patients had AST levels above the abnormal range but not higher than 1.8X ULN; in fact most elevated levels were close to the upper limit of normal.<sup>135</sup>

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<sup>132</sup> Twenty-one patients had LDH levels measured prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

<sup>133</sup> They were 20 elevations in patient 18002, seventeen elevation in patient 18003, fourteen elevations in patient 10901, 13 elevations in patient 18001, 11 elevations in patient 10902, 10903, and 10908, 10 elevations in patients 10906 and 18006, 9 elevations in patients 10905, 18004, 18007, and 18009, 8 elevations in patients 10907 and 18005, 7 elevations in patients 10904, 18008, 18010, 18011, 18012 and 18013, and 4 elevations in patients 10909 and 10910.

<sup>134</sup> 15/27 (55%) at baseline, 10/29 (34%) at Year 1, 8/26 (30%) at Year 2, 5/21 (23%) at Year 3, 4/21 (19%) at Year 4, 5/18 (27%) at Year 5, 3/15 (20%) at Year 6, 4/17 (23%) at Year 7, 1/11(9%) at Year 8, 4/8 (50%) at Year 9, 2/8 (25%) at Year 10, 1/5 (20%) at Year 11, and 0/3 (0%) at Year 12.

During the trial, 83 above-normal AST elevations were recorded in 17 patients.<sup>136</sup> None were >3X ULN. In fact only 7 measurements in 6 patients were >2X ULN and the highest was 2.4X ULN.<sup>137</sup>

## ALT

A few subjects had elevated ALT levels at various timepoints during the clinical trial but none at baseline.<sup>138</sup> Applicant's presentation of ALT results is summarized as follows:

- ALT was normal at baseline for all 23 subjects; it remained normal for 17 of these subjects during long-term mecasermin treatment.
- one subjects (18-001) had AST and ALT elevations (216 U/L and 78 U/L, respectively) on one occasion; the subject was also receiving antibiotics and decongestants for otitis media and Tegretol for seizure disorder.
- one subject (10-909) had "ongoing mild elevations in AST from baseline and one concomitant elevation of ALT after approximately 3 years of therapy."
- four subjects had more than 2 elevations in both AST and ALT during long-term treatment (10-907, 18-006, 10-904 and 10-905); the first two had elevations which were <2X ULN (in fact they were only slightly above the reference range); the latter two had on at least one occasion AST/ALT elevations 3-5X ULN that could not be explained and which either normalized (patient 10-905) or remained < 2X ULN (10-904).

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<sup>135</sup> Twenty-five patients had AST levels measured prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

<sup>136</sup> They were 10 elevations for subject 18003, 9 elevations for subjects 10905 and 18006, eight elevations for subject 10904, 18001, seven elevations for subjects 10909 and 18012, five elevations for subject 18004, four elevations for 18001, three elevations for subject 18005, two elevations for subjects 10907, 10908, 10913, 18808, 18809 and 18010 and one elevation in subject 18013.

<sup>137</sup> The patients were 10904 (2.1 ULN twice), 10909 (2.2X ULN), 18001 (2.1X ULN), 18003 (2.1X ULN), 18004 (2.4X ULN), and 18006 (2X ULN).

<sup>138</sup> 0/24 (0%) at baseline, 1/28 (3%) at Year 1, 1/27 (3%) at Year 2, 3/23 (13%) at Year 3, 3/20 (15%) at Year 4, 3/17 (17%) at Year 5, 1/15 (6%) at Year 6, 1/16 (6%) at Year 7, 1/8 (12%) at Year 8, 1/6 (16%) at Year 9, 1/6 (16%) at Year 10, 1/3 (33%) at Year 11, 0/1 (13%) at Year 12.

The applicant comments in the 120-day safety update that

transient mild-to-moderate increases in liver function tests were common in children treated with rhIGF-1. They were asymptomatic and were not associated with cholestasis; test values returned to normal as treatment continued.

This reviewer adds the following observations:

All baseline ALT measurements were within normal range.<sup>139</sup> Six subjects had ALT elevations during treatment (Table #); of them, two had single elevations and four subjects had more than 2 elevations.

**Table #: High ALT values during the trial**

Patient ID	Study Year	Result in IU (XULN)
10904	2.52	64.0 H (2.1)
10904	4.06	98.0 H (2.5)
10904	4.55	143.0 H (3.6)
10904	5.05	265.0 H (5.5)
10904	5.57	75.0 H (1.5)
10904	6.60	76.0 H (1.5)
10905	1.05	33.0 H (1.1)
10905	2.02	44.0 H (1.4)
10905	2.52	37.0 H (1.2)
10905	3.54	98.0 H (2.5)
10905	4.06	78.0 H (2)
10905	4.55	76.0 H (1.9)
10905	5.05	202.0 H (4.2)
10907	4.10	39.0 H (1)
10907	4.56	42.0 H (1)
10907	5.048	41.0 H (1)
10907	6.49	87.0 H (1.2)
10909	2.87	78.0 H (1.6)
18001	0.50	78.0 H (2)
18006	5.45	40.0 H (1.1)
18006	8.15	40.0 H (1.1)
18006	9.07	75.0 H (2.1)
18006	10.07	40.0 H (1.1)

Source: XLAB Dataset

IU = international units. ULN = upper limit of normal.

<sup>139</sup> Twenty-one patients had ALT levels measured prior to mecaseimerin administration at/or prior to baseline. Some had more than one measurement provided.

Patient 10904 had normal ALT at baseline (27 IU) and normal LFTs for the next 3 measurements during the following 2 years, followed by continued elevated values: 64 IU at 2.5 years, 98 IU at 4.0 years, 143 IU at 4.5 years, 265 IU at 5.0 years, 75 IU at 5.5 years, and 76 IU at 6.6 years (end of trial participation).

Patient 10905 had normal ALT at baseline (23 IU), followed by several abnormal values for the next 5 years (33 IU, 44 IU, 37 IU, 98 IU, 78 IU, 76 IU and 202 IU) followed by normal values of 43 IU and 46 IU at 5.5 and 6.6 years of treatment. Patients 10904 and 10905 were twins; both had also multiple elevations in AST. The cause of the elevations in AST and ALT is unknown. They were the only patients with ALT elevations >3XULN.

Patient 10907 had normal ALT at baseline (15 IU), normal measurements for the first 3.5 years, minimally elevated ALT between years 4.1 and 5.0 (between 39 IU and 42 IU) followed by normal ALT at 5.5 years and a mild elevation at the time of discontinuation 6.4 years (87 IU).<sup>140</sup>

Patient 10909 had an isolated elevation in ALT to 70 IU at 2.8 years of treatment preceded and followed by normal ALTs.<sup>141</sup>

Patient 18001 had an isolated elevation in ALT to 78 IU at 0.5 years of treatment preceded and followed by normal ALTs.<sup>142</sup>

Patient 18006 had normal ALTs at baseline and through year 4.9 followed by mild elevations toward the end of treatment (40 to 75 IU).<sup>143</sup>

The 120-day safety update describes liver enzyme elevations in 2 patients enrolled in the investigator Study F0363s, a study of patients with non GH-deficient short stature and Laron Syndrome treated with mecasermin.<sup>144</sup>

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<sup>140</sup> According to the applicant “there was “no apparent relationship between the abnormal values for AST and ALT in this subject except at the last observation” and “no intercurrent illness or concomitant medications were reported during this period.”

<sup>141</sup> According to the applicant this patient had “ongoing mild elevations in AST from baseline and one concomitant elevation of ALT after approximately 3 years of therapy.

<sup>142</sup> The applicant points out that the patient was receiving “antibiotics and decongestants for otitis media and Tegretol® for seizure disorder”.

<sup>143</sup> This patient “had elevated AST at baseline that continued at the majority of observations.”

<sup>144</sup> One subject, a 15-year old with GH gene deletion and a history of mild transaminase elevations, had elevation of liver enzymes on 2 separate occasions after mecasermin administration. Reportedly, at the start of treatment, he had symptoms consistent with a viral illness (ie, rash, low grade fever, and upper respiratory tract symptoms). Following mecasermin dosing of 50 µg/kg SC BID, 100 µg/kg SC BID and 200 µg/kg SC BID on three successive days the liver enzymes were elevated (on Day 3); ALT evaluations over 11 days showed the following values: 48, 217, 229, 331, and 109 (AST elevations were 66, 180, 140, 335, 76). Liver enzymes were normal on two occasions after discharge. On a second admission 3 months later, mild elevation of liver enzymes was again noted at baseline; the patient received mecasermin at 50 µg/kg SC BID and further elevation of liver enzymes was noted following the third dosing (ALTs were 49, 84, 67, 475, and 35, respectively; ASTs were 63, 109, 52, 484, and 33, respectively).

One patient with GH gene deletion enrolled in an investigator-sponsored study was described as having LFT elevation after mecasermin treatment and on rechallenge. s at baseline and subsequent increased liver function tests on Day 3 of mecasermin treatment. This patient had a similar response when re-challenged three months later (LFT elevation on Day 3 of mecasermin treatment).

### **Total bilirubin**

There was a single above-normal bilirubin measurement at Year 3.

### **Renal function**

#### **Creatinine**

There were no creatinine values above the upper limit of normal at any time during treatment.

#### **BUN**

Nine measurements in 8 patients at baseline and 38 measurements out of 383 collected in 16 patients (BUN range: 18 to 35 mg/dl) were elevated.<sup>145</sup> Most of the mild elevations were followed by normal values. Importantly, none were  $\geq 2X$  ULN and none of these elevations were accompanied by out-of-range creatinine elevations.

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Mecasermin was discontinued. An extensive work-up for viral, autoimmune, and metabolic liver disease was reportedly, negative. A liver biopsy was performed and showed focal hepatocellular necrosis with a neutrophilic infiltrate ("according to the pathology report these findings were "non-specific but compatible with a medication reaction." The events were considered to be related to mecasermin by the investigators. Another subject, a 9-year old girl enrolled in a non-GH deficient short stature study had elevation of liver enzymes on one occasion during treatment with mecasermin (this subject also had mild liver enzyme elevation at baseline with unknown etiology and also had a history of viral illness). She developed a rash and mildly elevated transaminases after 6 doses of rhIGF-I. A biopsy of the rash was consistent with a drug reaction. The subject was dropped from the study. No drug re-challenge was performed. A third subject (with Laron Syndrome, Study F0363s) had documented sleep apnea, pulmonary hypertension and cardiomegaly.

<sup>145</sup> Several patients had BUN elevations at baseline and at various times during the clinical trial. 10/33 (30%) at baseline, 3/33 (9%) at Year 1, 3/31 (9%) at Year 2, 5/26 (19%) at Year 3, 3/23 (13%) at Year 4, 3/18 (16%) at year 5, 2/16 (12 %) at Year 6, 2/13 (11%) at Year 7, 1/11 (9%) at Year 8, 0/9 (9%) at Year 9, 1/8 (12 %) at Year 10, 0/6 (0%) at Year 11, and 0/3 (0%) at Year 12.

## Calcium and phosphorus

Very few calcium measurements were outside the normal range.<sup>146</sup> Several patients had above and below normal serum phosphate levels at different timepoints within the clinical trial.<sup>147</sup> The applicant states that “calcium and phosphorus levels were generally normal during treatment.”

This reviewer’s analysis of the “flagged” abnormal calcium levels indicated that most levels were within the normal range; six measurements were below normal and nine measurements were above normal. The “low” levels ranged from 7.3 to 8.7 mg/dl and the “high” levels ranged from 10.1 to 11 mg/dl. For most patients these out-of-range values were followed by normal levels.<sup>148</sup>

This reviewer’s analysis of the phosphorus serum concentrations indicates that most measurements were within the normal range. There were also 16 phosphorus measurements flagged as “low” (out of 333 total number of measurements) in 10 patients (range 2 to 3.9 mg/dL). Most abnormal values (including the most extreme values) were associated with normal subsequent measurements.<sup>149</sup> Fifty-one of the 333 phosphorus measurements were flagged as “high” in 13 patients (range: 4.5 to 6.7 mg/dL).

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<sup>146</sup> The only timepoints when serum calcium levels were elevated were Year 1 (2/29 patients or 6%) and Year 3 (2/20 or 10%). There were no above normal calcium measurements at any of the other timepoints between baseline and Year 12. Low serum calcium were reported at the following timepoints: baseline (1/29 or 3% patients), Year 1 (1/29 or 3%), Year 4 (1/20 or 50%), Year 7 (1/17 or 5%) and Year 10 (1/8 or 12%). There were no below calcium levels at the other timepoints.

<sup>147</sup> Elevated phosphate levels were found in 0/24 (0%) at baseline, 3/26 (11%) at Year 1, 3/27 (11%) at Year 2, 4/24 (16%) at Year 3, 4/21 (19%) at Year 4, 5/17 (29%) at Year 5, 4/14 (28%) at Year 6, 6/17 (35%) at Year 7, 1/11 (9%) at Year 12, 0/8 (0%) at Year 9, 2/8 (25%) at Year 10, 2/6 (33%) at Year 11, and 0/3 (0%) at Year 12. Below normal Phosphate levels were reported in 2/24 (8%) patients at baseline, 3/26 (11%) at Year 1, 1/27 (3%) at Year 2, 1/24 (4%) at Year 3, 1/21 (4%) at Year 4, 0/17 (0%) at Year 5, 1/16 (7%) at Year 6, 2/17 (35%) at Year 7, 0/11 (0%) at Year 8, 2/8 (25%) at Year 9, 0/8 (0%) at Year 10, 0/6 (0%) at Year 11, and 0/3 (0%) at Year 12.

<sup>148</sup> Of the patients with low levels at one time or other, all had normal follow-up calcium concentrations with the exception of patient 18001 who had a calcium level of 8.2 mg/dL at the last measurement of trial after 9.9 years of mecasermin (all prior calcium levels on trial were normal).

<sup>149</sup> The most extreme values observed on patient 10906 (3.1 and 2.2 at 0.5 and 1 year on trial, respectively) were followed by normal measurements for the remainder of the trial (last on-trial measurement at 11.4 years of therapy).

## Sodium, chloride and potassium

There were several and generally few above- and below-normal measurements for serum sodium,<sup>150</sup> chloride,<sup>151</sup> potassium,<sup>152</sup> and CO<sub>2</sub>.<sup>153</sup>

This reviewer's analysis of the on-trial abnormal sodium levels shows that there were 8 below normal measurements in 6 patients; they ranged between 130 and 136 mEq/L. There were 6 above-normal sodium measurements in 5 patients (range: 144 to 147 mEq/L). Analysis of the potassium levels indicate that there were 8 below-normal levels in 6 patients (range: 3-3.5 mEq/L) and 46 high levels in 32 patients.<sup>154</sup> There were 40 above normal chloride measurements in 24 patients (range: 108 to 121 mEq/L) and 39 below normal measurements in 8 patients (range 100 to 108 mEq/L). Analysis of serum CO<sub>2</sub> levels shows that there were no above-normal measurements; 42 below normal CO<sub>2</sub> levels were recorded in 11 patients (range: 12 to 23 mEq/L).

## Carbohydrate metabolism

A few patients had low or elevated glucose levels at baseline or during the clinical trial.<sup>155</sup> The applicant reports that serum glucose was "normal in the majority of serial

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<sup>150</sup> Above normal serum levels were observed in 1/22 (4%) patients at year 4, 1/11 (9%) at Year 8, and 2/8 (25%) at Year 10. There were no other above-normal measurements at any of the other visits thorough Year 12. Below normal sodium levels were recorded in 3/33 (9%) of patients at baseline, 3/33 (9%) patients at Year 1, 1/22 (4%) at Year 4, 1/11 (9%) at Year 8, and 1/9 (11%) at Year 9. There were no other below-normal measurements at any of the other visits thorough Year 12.

<sup>151</sup> Above-normal serum chloride levels were recorder in 6/28 (21%) of patients at baseline, 4/25 (16%) at Year 1, 4/26 (15%) at Year 2, 1/19 (5%) at year 3, 3/20 (15%) at year 4, 2/18 (11%) at Year 5, 3/16 (18%) at Year 6, 0/12 (0%) at Year 7, 0/11 (0%) at Year 8, 1/9 (11%) at year 9, 2/8 (25%) at Year 10, 1/6 (16%) t year 11, and 0/3 (0%) at Year 12. Below-normal chloride levels were observed in 7/28 (25%) of patients at baseline, 5/25 (20%0 at Year 1, 6/26 (23%) at Year 2, 3/19 (15%) at Year 3, 1/20 (5%) at Year 4, and none at any other timepoint through Year 12.

<sup>152</sup> Above-normal potassium levels were observed in 3/3 (9%) patients at baseline, 6/33 (18%0 at Year 1, 6/31(19%) at Year 2, 3/24 (12%) at Year 3, 1/22 (4%) at Year 4, 0/18 (0%) at Year 5, 0/16 (0%) at year 6, 0/12 (0%) at Year 7, 2/11 (18%) at Year 8, 0/9 (0%) at Year 9, 1/8 (12%) at Year 10, 1/6 (16%) at Year 11, and 1/3 (33%) at Year 12. Below-normal potassium levels were recorded in 1/12 (8%) of patients at year 7, 2/11 (18%) at year 8, 2/9 (22%) at year 9, 2/8 (24%) at year 10, and 1/6 (16%) at Year 11; no below-normal potassium levels were recorded at any other visits between baseline and Year 12.

<sup>153</sup> There were no above-normal CO<sub>2</sub> measurements during any on-trial measurement. Below-normal CO<sub>2</sub> measurements were observed in 10/13 (75 % patients at baseline, 8/10 (80%0 at Year 1, 7/12 (58%) at Year 2, 3/6 (50%) at Year 3, 1/5 (20%) at Year 4, 0/7 (0%) at Year 5, 1/8 (12%) at Year 6,1/7 (9%) at year 7, and none for Years 8 through 12.

<sup>154</sup> Potassium measurements in blood specimens are often and notoriously unreliable in children due the difficulty in blood drawing and the subsequent sample hemolysis (the range of elevated potassium levels was 4.8 to 9.1 mEq/L).

<sup>155</sup> Below normal glucose values were observed in 11/36 (30%) patients at baseline, 4/34 (11%) patients at Year 1,

samples except for occasional mild elevations that may have represented post-prandial sampling. Glycosylated hemoglobin (HgbA1c) levels were generally normal with the exception of four subjects who had sporadic increases in HgbA1c.<sup>156</sup>

This reviewer's analysis adds the following observations:

At baseline, 12 patients reported 14 "low" glucose levels (range: 29 and 64 mg/dL; most levels were in the 40's and 50's); two other patients (18001 and 18004) had above-normal glucose levels of 140 and 131 mg/dL, respectively.<sup>157</sup> Thirty-seven patients had 576 glucose measurements done while on mecasermin treatment (range for number of measurements: 1 to 38). Of them, 15 patients had 25 below-normal glucose levels (range: 20 to 64 mg/dL)<sup>158</sup> and 14 patients had above-normal glucose measurements (range 112 to 297 mg/dL; nine subjects had glucose concentrations above 150 mg/dL). Importantly, there were no cases of diabetes diagnosed on trial.

### **Thyroid function**

Overall, there were few out of range T4/TSH measurements. The applicant states that the thyroxine (T4) measurements were reported generally as normal except for three subjects; all three, reportedly, had normal measurements at follow-up visits. One subject (18-005) received thyroid replacement therapy for approximately 3 months. For the other 2 subjects thyroid function tests normalized at follow-up without thyroid hormone replacement.

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4/34 (11 %) at Year 2, 2/25 (8%) at Year 3, 1/20 (5%) at Year 4, 1/17 (5%) at Year 5, 1/13 (7%) at Year 6, 0/12 (0%) at Year 7, 0/11 (0%) at Year 8, 0/8 (0%) at Year 9, 1/8 (12%) at Year 10, 0/6 (0%) at Year 11, and 0/3 (0%) at Year 12. Above normal serum glucose levels were observed in 0/36 (0%) patients at baseline, 2/34 (5%) at Year 1, 1/34 (2%) at Year 2, 3/25 (12%) at Year 3, 2/20 (10%) at Year 4, 1/17 (5% at Year 5), 0/13 (0%) at year 6, 0/12 (0%) at Year 7, 0/11 (0%) at Year 8, 1/8 (12%) at Year 9, 0/8 (0%) at year 10, 1/6 (16%) at Year 11, and 0/3 (0%) at Year 12.

<sup>156</sup> Two subjects had two consecutive increased levels of HgbA1c early in treatment that subsequently normalized. One subject (18-001) had decreased values of HgbA1c (3.3 to 4.6 %) in addition to intermittent dizziness, disorientation and generalized seizures.

<sup>157</sup> Thirty-three patients had glucose measurements before mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

<sup>158</sup> Two patients (18001, and 18005) had glucose levels of 20 mg/dL and 24 mg/dL, respectively; 10 patients had 10 glucose measurements >30 but <50 mg/dL (patients 18001, 18003, 18013, 18005, 18012, 18001, 18003, 10908, 18001, and 18009); seven patients had glucose concentrations >= 50 but < 60 mg/cL; 4 patients had 6 glucose concentrations >= 60 mg/dL but < lower limit of normal.

This reviewer's analysis adds the following observations:

#### **T4**

At baseline there were there were two measurements in two patients were above the upper limit of normal<sup>159</sup> and two measurements in one patient were below the lower normal limit.<sup>160</sup>

Twenty-seven patients had 262 measurements for T4 done during the mecasermin treatment (the number of measurements ranged between 2 and 15). Of these, 18 measurements in 7 patients were above normal (range 11.5 to 18.3 µg/dL) and 6 measurements in 4 patients were below normal.<sup>161</sup>

#### **TSH**

At baseline, eight measurements in seven patients were above normal (range: 6 to 11.8 µU/mL); none was below normal range.<sup>162</sup>

Twenty-eight patients had 256 TSH measurements on mecasermin treatment (range of measurements: 1 to 15); of these, six measurements in five patients were above normal (range: 5.5 to 6.2). There was only one isolated low TSH measurement (0.1 µU/mL for patient 18008; prior and subsequent measurements in this patient were normal).

#### **Total cholesterol and triglycerides**

A relatively large proportion of patients had elevated cholesterol levels at baseline and at various timepoints during the clinical trial.<sup>163</sup> A similar pattern was observed for

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<sup>159</sup> Patients 10951 and 19010 had T4 serum concentrations of 11.4 µg/dL and 13.5 µg/dL, respectively.

<sup>160</sup> Patient 18005 had before treatment T4 serum concentrations of 7.1 and 5.2 µg/dL)

<sup>161</sup> Patient 10908 had T4 of 2.5 and 1.3 at 7.5 and 9 years of treatment, respectively (no TSH values are available for these timepoints; subsequent T4 was 7.1 at 11 years of treatment/end of study). Patient 18001 had a T4 of 6.3 and 7.1 at 1.6 and 2.1 years of treatment, respectively. Patient 18005 had a T4 of 6.4 at 0.7 years of treatment. Overall, twenty-seven patients had T4 measurements done prior to mecasermin administration at/or prior to baseline. Some had more than one measurement provided.

<sup>162</sup> Twenty-seven patients had TSH measurements done prior to mecasermin administration at/or prior to baseline (most patients had one measurement, few had more than one).

<sup>163</sup> Cholesterol levels were elevated in 12/34 (35%) patients at baseline, 14/33 (42%) at Year 1, 17/31 (54%) at Year 2, 12/23 (52%) at Year 3, 13/24 (54%) at Year 4, 10/17 (58%) at Year 5, 5/13 (38%) at Year 6, 6/17 (35%) at Year 7, 8/11 (72%) at Year 8, 2/8 (25%) at Year 9, 2/8 (25%) at Year 10, 4/6 (66%) at Year 11, and 2/3 (66%) at Year 12.

triglycerides.<sup>164</sup> The applicant states that for total cholesterol and triglyceride levels (which were followed in 32 subjects, for up to 10 years in some) the levels of both analytes were reported to increase with age and showed considerable variability between individual measurements. Several patients had marked increases in cholesterol. For subject (10-909), the total cholesterol rose from 134 mg/dL to 277 mg/dL over approximately 8 years. This rise was accompanied by a more modest rise in triglycerides from 80 mg/dL to 120 mg/dL. Two other subjects (10-951 and 10-952) who had elevated total cholesterol at baseline (241 and 249 mg/dL, respectively) had further increases to 293 and 275 mg/dL, respectively, over the course of ~1 year. Triglycerides were, reportedly, elevated at baseline in both subjects (~175 mg/dL) (no follow-up triglyceride measurements were available). Two subjects (10-903 and 18-006) had, reportedly, an increase in triglycerides which was not accompanied by a “consistent rise in total cholesterol.” The applicant points out that elevations in total cholesterol, as well as LDL-cholesterol, have been reported previously in Primary IGFD in several publications.<sup>165</sup>

This reviewer’s analysis adds the following observations:

### **Total cholesterol**

At baseline, thirteen measurements in twelve patients were above normal (range: 187 to 249 mg/dL).<sup>166</sup> Three measurements in three patients were below normal (range: 104 to 137 mg/dL).

On mecasermin treatment, thirty-four patients had 313 cholesterol evaluations (range of number of measurements: 1 to 22). Of these, twenty-eight patients had 153/33 (approximately 50%)

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<sup>164</sup> 4/34 (11%) patients had elevated triglyceride levels at baseline, 4/30 (13 %) at Year 1, 6/29 (20%) at Year 2, 7/21 (33%) at Year 3, 7/22 (31%) at Year 4, 8/17 (47%) at Year 5, 3/13 (23%) at Year 6, 5/12 (41%) at Year 7, 4/11 (36%) at Year 8, 4/9 (44%) at Year 9, 2/8 (25%) at Year 10, 2/6 (33%) at Year 11, and 1/3 (33%) at Year 12.

<sup>165</sup> Specifically, for a cohort of patients with primary IGFD published by Laron and Klinger; the mean ( $\pm$ SEM) baseline serum cholesterol level was  $175.7 \pm 13.2$  mg/dL at baseline and was followed after 12 months of mecasermin therapy by a mean of  $191.6 \pm 11.3$  mg/dL.

<sup>166</sup> Thirty-two patients had total cholesterol measurements done prior to mecasermin administration at/or prior to baseline (most patients had one measurement, few had more than one).

elevated cholesterol measurements; 14 measurements in 9 patients were  $\geq 250$  and  $< 300$  mg/dL; only one measurement was over 300 mg (patient 10912: 336 mg/dL at one year of treatment); 77 measurements in 22 patients were  $\geq 200$  but less than 250 mg/dL; 21 patients had 61 measurements above upper normal limit but less than 200 mg/dL. Six patients had cholesterol levels below normal in 19 measurements (range 88 to 168 mg/dL). Overall, 141 measurements in 27 patients were in the normal range. The remarkable heterogeneity in serum total cholesterol levels in patients with primary IGFD is well documented (Laron Z and Klingler B, referenced above).

### **Triglycerides**

At baseline, 7 patients had 10 measurements above normal at baseline (range: 89 to 183 mg/dL). None had low triglyceride levels.<sup>167</sup>

On trial, 31 patients had 299 triglyceride measurements (range of number of measurements per patient: 1 to 22). Of these, two measurements in 2 patients were below normal: 12 mg/dL in patient 18004 (this was followed by normal values) and 26 mg/dL in patient 10908 (this was the last value on trial and was, inconsistent with the values collected over 9 years of treatment). Twenty-six patients had a total of 70 triglyceride measurements above the upper limit of normal.<sup>168</sup>

### **Alkaline phosphatase**

One patient had elevated alkaline phosphatase levels at baseline and several during the clinical trial.<sup>169</sup> There were 26 above-normal measurements during the trial in 14 patients (range: 129 to 959; most measurements were less than 200 with only four measurements above this threshold.<sup>170</sup>

#### *7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

### **Hematology**

There were no marked outliers or dropouts for abnormal hemoglobin concentrations and/or abnormal platelet counts.

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<sup>167</sup> Thirty-two patients had triglyceride measurements done prior to mecaseimerin administration at/or prior to baseline (most patients had one measurement, few had more than one).

<sup>168</sup> Fifteen patients had 31 measurements over 150 mg/dL. Four patients had levels over 300 mg (364 mg/dL in patient 10911, 304 mg/dL in patient 18006, 430 mg/dL in patient 18008, and 323 mg/dL in patient 18012).

<sup>169</sup> Elevated alkaline levels were recorded in 1/29 (3%) at baseline, 2/28 (7% at Year 1, 1/28 (3%) at Year 2, 2/23 (8%) at Year 3, 3/20 (15%) at Year 4, 2/18 (11%) at Year 5, 2/14 (14% at Year 6, 3/17 (17%) at Year 7, 1/8 (9%) at year 8, 0/7 (0%) at year 9, 0/8 (0%) at Year 10, 1/5 (20%) at Year 11, and 0/3 (0%) at Year 12.

<sup>170</sup> Patient 10905 had measurements of 303, 325 and 959, respectively; patient 18005 had a measurement of 758 U/L).

**Liver function tests**

Two subjects who had LFT elevations > 3X ULN on one and two occasions, respectively, are summarized in applicant’s Tables 13.4.2-3 and 13.4.2-4. They are twin sisters with GH gene deletion who had “minor elevations in AST prior to beginning therapy with mecasermin;” one of them (subject 10-904) also had an elevation in LDH prior to therapy. The ALT levels were mildly elevated for a few years prior to reaching their respective peak levels; subsequently they returned to normal or near normal levels, respectively, without interruption of mecasermin treatment. No specific diagnosis was made during the time of elevated ALT (and associated AST elevations). The

Table 13.4.2-3: Liver function Tests (Subject 10-904)

Subject ID	Time (yrs)	Age (yrs)	Mecasermin dose (µg/kg) SC BID	AST	High Reference Range (U/L)	ALT	High Reference Range (U/L)
10-904	-0.0	8.2	0	44 *	26	27	30
	0.6	8.8	120	42 *	26	22	30
	1.1	9.3	120	50 *	26	25	30
	2.0	10.2	80	37 *	26	28	30
	2.5	10.7	80	55 *	26	64 *	30
	4.1	12.3	120	90 *	41	98 *	39
	4.6	12.8	120	73 *	41	143*	39
	5.1	13.3	120	120*	41	265 *	48
	5.6	13.8	120	35	41	75 *	48
	6.6	14.8	120	57 *	38	76 *	48

Table 13.4.2-4: Liver function Tests (Subject 10-905)

Subject ID	Time (yrs)	Age (yrs)	Mecasermin dose (µg/kg) SC BID	AST	High Reference Range (U/L)	ALT	High Reference Range (U/L)
10-905	-0.0	8.2	0	39 *	26	26	30
	0.6	8.8	120	36 *	26	23	30
	1.1	9.3	120	36 *	26	33 *	30
	2.0	10.2	80	40 *	26	44 *	30
	2.5	10.7	80	44 *	26	37 *	30
	3.5	11.7	120	63 *	41	98 *	39
	4.1	12.3	120	45 *	41	78 *	39
	4.6	12.8	120	75 *	41	76 *	39
	5.1	13.3	120	114*	41	202*	48
	5.6	13.8	120	32	41	43	48
	6.6	14.8	120	51 *	38	46	48

\* value above upper limit of normal

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applicant states that “the cause of the elevations in AST and ALT is unknown.”

In addition one subject had LFT elevation in an investigator-sponsored clinical trial that re-occurred during re-challenge (See detailed description in previous section).

**Renal function**

### **Creatinine**

There were no marked outliers in creatinine measurements.

### **BUN**

There were no marked outliers in BUN measurements.

### **Calcium**

There were no marked outliers in serum calcium measurements.

### **Phosphorus**

There were no marked outliers in serum phosphorus measurements (one isolated low phosphorus measurement of 2 mg/dL was recorded in one patient but normalized on trial medication; the significance, if any, of this measurement is unknown).<sup>171</sup>

### **Carbohydrate metabolism**

Two very low blood glucose levels (20 and 24 mg/dL, respectively) were observed, as were other 10 measurements in the 30-50 mg/dL range. These observations are consistent with the known hypoglycemic effect of IGF-I and corroborate the risk of hypoglycemia that was observed clinically (refer also to the analysis of hypoglycemia in Section 7.1.5.5).

### **Thyroid function**

There were no marked outliers in T4 and TSH measurements.

### **Total cholesterol and triglycerides**

Remarkable variability and elevation in total serum cholesterol and triglyceride serum concentration were observed during the trial.<sup>172</sup>

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<sup>171</sup> Rapid fall in serum phosphorus has been described with the intravenous injection of IGF-I but it is not expected to occur in association with subcutaneous administration. The timing of the blood collection with respect to mecasermin administration is not known.

<sup>172</sup> The applicant concluded that: "It remains unclear whether the rises in total cholesterol observed in some subjects in this study represent a direct effect of mecasermin treatment, or whether the rise is associated with an absence of GH-action due to the severe nature of their Primary IGFD that is unrelieved by mecasermin treatment."

#### 7.1.7.4 Additional analyses and explorations

Additional analyses of laboratory data have been integrated in the previous section. For comments on the time-dependency of adverse events with respect to mecasermin treatment refer to the review of hypoglycemia in Section 7.1.5.5. There were no distinct patterns of dose-dependent adverse events.

#### 7.1.7.5 Special assessments

The issue of risk of potential hepatotoxicity has been reviewed detail in Sections 7.1.7.3.2 and 7.1.7.3.3 (analysis of ALT elevation in several patients).

### 7.1.8 Vital Signs

#### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs (including pulse and blood pressure measurements) were, reportedly, routine clinical evaluations in all mecasermin studies.

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable (there was no control group).

#### 7.1.8.3 Standard analyses and explorations of vital signs data

##### *7.1.8.3.1 Analyses focused on measures of central tendencies*

Vital signs in study F0671 are summarized in Table 20, which re-formats applicant's Table 13 of 5.3.5.2.3 Study Report F0671g. The mean pulse and blood pressure did not show any clinically meaningful changes for up to 24 months. The standard deviations remained also constant on treatment and were comparable to those measured for baseline values. The range of measurements did not suggest any outlier measurements. In the 120-day safety update the applicant provides vital signs data for up to 12 years (after 7-8 years the number of patients on trial was in single digits). The changes observed (a reduction in mean pulse rate and a small increase in mean systolic and diastolic blood pressure) were consistent with to-be-expected age-related changes. These findings are consistent with those provided by an extended dataset submitted with the 120-day safety update in 32 patients.

**Table 20: Vital signs in Study F0671**

Variable	Baseline	Month 6	Month 12	Month 18	Month 24
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<b>Pulse (/min)</b>					
No.	23	23	23	23	23
Mean (SD)	100 (17.4)	96 (12.9)	96 (15.8)	99 (16.6)	95 (12.8)
Median	96	94	94	96	98
Range	76 -158	68 -123	70 -131	70 -127	76 -122
<b>Systolic BP (mm Hg)</b>					
No.	22	23	23	23	23
Mean (SD)	97 (11.0)	92 (10.9)	96 (12.4)	95 (9.6)	98 (15.4)
Median	95	94	98	95	97
Range	78 -114	72 - 115	71 -120	81 -115	7- 127
<b>Diastolic BP (mm Hg)</b>					
No.	22	23	23	23	23
Mean (SD)	54 (8.5)	53 (9.5)	56 (8.3)	58 (7.8)	56 (10.7)
Median	52	52	55	57	58
Range	41 -72	38 -73	42 -75	45 -74	37 -73

Source: Table 13 of 5.3.5.2.3 Study Report F0671.

#### 7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Refer to Section 7.1.8.3.1, above.

#### 7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

Refer to Section 7.1.8.3.1, above. There were no marked outliers or dropouts for vital sign abnormalities.

#### 7.1.8.4 Additional analyses and explorations

No additional analyses or explorations of vital signs were performed.

### 7.1.9 Electrocardiograms (ECGs)

#### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

This reviewer has not identified a presentation of ECG results in the submission other than a reference in Study F0375g located in the Special Safety Assessments section, where the applicant notes that ECGs were performed during the open-label period and were normal. In the 120-day safety update, in response to a request of additional ECG information in Study 1419', the applicant states that "ECG analyses were not done."

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Section 7.1.9.1.

#### 7.1.9.3 Standard analyses and explorations of ECG data

Refer to Section 7.1.9.1.

##### *7.1.9.3.1 Analyses focused on measures of central tendency*

Refer to Section 7.1.9.1.

##### *7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Refer to Section 7.1.9.1.

##### *7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities*

Refer to Section 7.1.9.1.

#### 7.1.9.4 Additional analyses and explorations

This reviewer's search in the XSPECTST dataset identified 14 normal ECGs done in 13 patients. All were done prior to mecasermin treatment..

#### 7.1.10 Immunogenicity

The potential for anti-IGF-I antibody formation was studied in four clinical studies: F0206s, F0375g, F0632g, and F0671g. In these studies mecasermin was administered at doses of 80 to 120  $\mu$ /kg BID. Antibody formation was evaluated with an ELISA assay. Twenty-two subjects had antibody titers measured at one or more times during the first year of treatment; eleven of them (50 %) had positive antibody titers at various (but not all) measurements during the first year of treatment. In follow-up Study F0671 antibody titers were followed for 2 years and did not increase in titer. The mean height velocity of  $7.3 \pm 3.1$  cm/yr during the first year of therapy in the 11 subjects without antibodies was comparable to the mean height velocity of  $7.9 \pm 2.1$  cm/yr observed in 11 patients with antibodies (p-value = 0.54). The applicant reports that "despite up to 10 years exposure to mecasermin, there were no apparent

immunotoxicity safety concerns detected at the proposed for market clinical dosing regimen.” There were no allergic reactions reported among the adverse events collected during the primary IGFD program.

#### 7.1.11 Human Carcinogenicity

There were no reports of malignancies associated with mecasermin during the primary IGFD clinical program. However, IGF-I is a growth factor that plays a central physiologic role in the control of body growth; consequently, mecasermin treatment in primary IGFD should be aimed at restoring physiologic IGF-I levels (replacement therapy). Measurement of IGF-I serum concentrations during clinical trial 1419 indicates that the mean two-hour post dose serum concentrations of IGF-I, although higher relative to the pre-dose concentrations, do not exceed the low normal range. Specifically, the post-dose SD score for serum IGF-1 was  $-2.1 \pm 2.6$  for the 80 µg/kg dose and  $-1.7 \pm 2.0$  for the 120 µg/kg dose.<sup>173</sup>

#### 7.1.12 Special Safety Studies

Not applicable.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

No formal studies have been conducted to examine withdrawal phenomena or drug abuse. However, based on our current understanding of IGF-I’s mechanism of action there is no theoretical basis to suspect drug dependence for mecasermin. No drug dependence has been described for somatropin (recombinant human growth hormone), a physiologically related compound and an approved drug product with worldwide clinical experience close to 200,000 patients accumulated for over 4 decades.

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<sup>173</sup> Out of 164 pre-dose serum IGF-I measurements done in 34 patients, there were only two IGF-I SD score measurements greater than 2 (3.3 and 5.6 respectively; they both occurred in one patient). Out of 122 two hour post-dose measurements there were only 8 measurements in 5 patients where the IGF-I serum concentration SDS was greater than 2 ( 2.3, 2.9, 2.3, 4.4, 3.2, 3.8, 3.3, and 4.0); they distributed equally between the lower doses (60-80 µg/kg) and higher doses (120 µg/kg).

Since rhIGF-I is an anabolic hormone, mecasermin has the theoretical potential of abuse similar to that of growth hormone. The hypoglycemic effect of mecasermin may act as a deterrent for such use.

#### 7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies reported during the study. The applicant states that

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 fetus. A negative pregnancy test and education about adequate contraception are recommended for all women of childbearing potential prior to treatment with mecasermin.

#### 7.1.15 Assessment of Effect on Growth

Linear growth is an efficacy endpoint for all the mecasermin clinical studies (see efficacy analyses).

#### 7.1.16 Overdose Experience

There were no cases of accidental overdose in the primary IGFD clinical trials. Almost all the clinical trial patient exposure occurred at doses below or equal to the highest to-be-marketed dose of 120 µg/kg BID. Based on the known insulinomimetic effect of IGF-I, it is to be expected that hypoglycemia is the adverse event that will most likely occur in cases of accidental mecasermin overdose.<sup>174</sup>

#### 7.1.17 Postmarketing Experience

Mecasermin is not an approved drug in the US. Therefore, there is no postmarketing experience with this drug. Refer also to Section 7.2.2.2

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<sup>174</sup> Syncope followed by a tonic/clonic seizure (associated with bradycardia and brief asystole) was experienced by a normal volunteer during a mecasermin/euglycemic clamp in Study F0355s. The episode occurred at the end of a mecasermin intravenous infusion of 1.8 mg given over 10 minutes.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Refer to Section 4.1 and 4.2 and 6.1.3

#### 7.2.1.1 Study type and design/patient enumeration

Refer to Sections 4.1, 4.2, and 6.1.3.

#### 7.2.1.2 Demographics

Seventy-one subjects received at least a dose of mecasermin. Of these, 43 (61%) were male and 28 (39%) were female. Fifty-eight (82%) were Caucasian, 3 (4%) African-American, 6 (8%) Hispanic, 3 (4%) Asian, and 1 (1%) were included in the "Other" category. Most patients (61 or 86%) had Laron Syndrome; 8 (11%) had GH gene deletion, 1 (1%) had antibodies to GH, and 1 (1%) had isolated genetic GH deficiency type 1A. Sixty one (86%) of patients were Tanner I, 1 (1%) was Tanner II, and 9 (13%) had Tanner stage unknown at the beginning of treatment. Sixty four (90%) were naïve to mecasermin treatment.

#### 7.2.1.3 Extent of exposure (dose/duration)

The drug exposure by dose is summarized in applicant's Table 13.1-1. The total exposure for the 71 patients enrolled was 274 patient-years. Most patients were exposed to the 120 µg/kg BID dose regimen (221 patient years or 81% of the total exposure) and to the 80 µg/kg BID dose regimen (31 patient years or 11% of the total exposure). Together, these doses accounted for 92 % of the total exposure. The mean duration of exposure was  $3.9 \pm 3.2$  years (median exposure: 3.0 years). Some patients were treated long-term. (up to or in excess of 10 years).<sup>175</sup>

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<sup>175</sup> The 120-day safety update adds 47 subject-years of drug exposure thus increasing the overall exposure to mecasermin to 321 patient-years as of April 7, 2005. The exposure to the 120 µg/kg BID dose regimen is 243 patient-years and to the 80 µg/kg BID dose regimen is 34 patient years.

**Table 13.1-1: Exposure to Mecasermin**

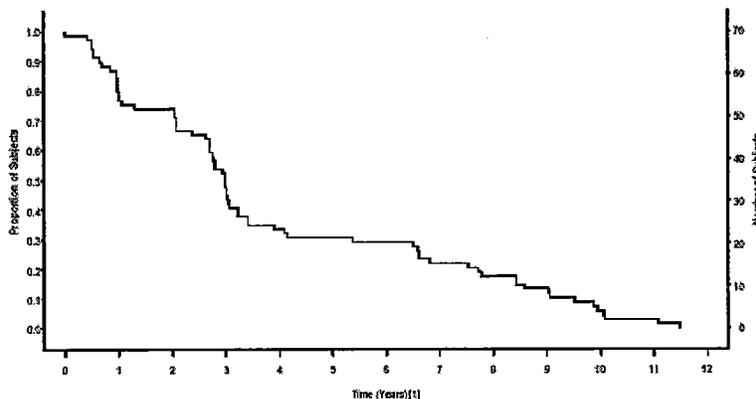
BID Dose	Patient Years
40 µg/kg	1
50 µg/kg	< 0.5
60 µg/kg	8
70 µg/kg	2
80 µg/kg	31
90 µg/kg	2
100 µg/kg	7
110 µg/kg	1
120 µg/kg	221
140 µg/kg	< 0.5
240 µg/kg	1
Total	274

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A Kaplan-Meier plot that illustrates the duration of treatment for the 71 patients enrolled is presented in applicant's Figure 13.1-1.

**Figure 13.1-1: Kaplan-Meier Plot of Mecasermin Treatment Duration- All Subjects (n=71)**



Source: Appendix 16.2.11.2

[1] Number of years from time of first dose of mecasermin therapy to time of last height measurement

In addition to patients with primary IGFD, mecasermin has been administered in multiple studies to a variety of patient populations including Type 1 diabetes (> 500 subjects), Type 2 diabetes (> 700 subjects), and HIV cachexia (11 subjects). Approximately 200 healthy volunteers and subjects with Type 1 and Type 2 DM participated in bioequivalence and clinical pharmacology studies of mecasermin.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.2.1 Other studies

As mentioned above, mecasermin has been investigated as a treatment modality in Type 1 diabetes (>500 subjects), Type 2 diabetes (> 700 patients), and HIV cachexia (11 patients). With the exception of SAEs, information from these three datasets is not analyzed in detail for a variety of reasons. Firstly, the population in these studies is mainly adult, while the primary IGFD population is exclusively pediatric. Secondly, the route of administration in many of these studies is intravenous, unlike the route of administration for this application which is subcutaneous. Finally and importantly, the adverse event profile for Type 1 and Type 2 diabetes and for HIV patients is influenced in such a fundamental way by the specifics of these diseases and their coexisting morbidities that it cannot be extrapolated to children with primary IGFD.

### 7.2.2.2 Postmarketing experience

Mecasermin is not an approved drug in the United States. The applicant states that

Other rhIGF-1 preparations have been successfully registered and cleared for use in pediatric patients with growth hormone insensitivity. We know of no unexpected safety issues that have arisen in over 10 years of commercial product availability. In 1994, mecasermin (Pharmacia, now Pfizer) was approved for the treatment of growth hormone insensitivity in pediatric 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 pediatric patients. The product is still marketed in Japan. We know of no unexpected postmarketing safety issues associated with the Fujisawa product.

### 7.2.2.3 Literature

The application relies entirely on original data. Published data are referenced only to provide scientific support and confirmation to various observations made in the mecasermin clinical program.

Additional efficacy and safety information contributed by published clinical studies of rhIGF-I conducted in patients with primary IGFD is summarized by this reviewer in Section 8.6.

### 7.2.3 Adequacy of Overall Clinical Experience

It should be recognized that primary IGF deficiency is an exceedingly rare disease. It has been estimated that the number of patients with Laron Syndrome worldwide is approximately 350. Even if one takes into consideration the relatively broader clinical definition proposed by the applicant for severe IGFD in the label (height SDS  $\leq$  3.0; basal IGF-I SDS  $\leq$  -3.0; normal or elevated growth hormone) the target population is still very small (currently estimated that approximately 12,000 patients in US and Europe). In this context, the number of patients with primary IGFD studied in the mecasermin development program (71) represents a considerable segment of the target population (approximately 20% of the Laron Syndrome population and 0.6% for the “extended” indication). Most importantly, the length of exposure to the drug (mean exposure of  $3.9 \pm 3.2$  years, median exposure of 3 years) is considerable; a few patients were followed for over 10 years or until they reached near-adult final height.

The major limitation of the mecasermin clinical trial is the absence of a control group, which makes an accurate interpretation of the incidence of adverse events difficult. This, however, is not necessarily a shortcoming of the clinical program; it is rather a consequence of the fact that conducting a placebo-controlled clinical trial of rhIGF-I would be unethical once rhIGF-I has been proved to increase height in this patient population. From an efficacy standpoint it is important to recognize that the natural course of this condition is relatively well characterized. Growth charts specific for patients with Laron Syndrome are currently available and patients with primary IGFD, if appropriately diagnosed, are not anticipated to exhibit spontaneous correction of their growth deficits. The consequence of this observation is that growth acceleration on mecasermin is drug-related.

Importantly, the applicant has characterized the efficacy of mecasermin over a range of doses that includes a minimally effective dose (60  $\mu$ g/kg) as well as doses that are clearly effective in improving linear growth (80-120  $\mu$ g/kg). In addition, the applicant has characterized a method of safe treatment initiation (i.e. gradual upward titration of mecasermin dose to tolerability, based on the absence of hypoglycemia). There were no exclusion criteria that could limit the relevance of the efficacy and safety observations.

Overall, the information accumulated in the primary IGFD clinical program for mecasermin is adequate to reach a regulatory decision.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See pharmtox. review.

### 7.2.5 Adequacy of Routine Clinical Testing

The clinical assessments and laboratory testing (which included routine and special assessments) was, in general, adequate. Adverse events were gathered in all clinical trials. Laboratory evaluations, which were performed only in a subgroup of patients (approximately 1/3 of the patients enrolled) were extensive and included standard hematology and chemistry tests and anti-IGF-I antibodies. The risk of organomegaly was evaluated with serial echocardiograms, abdominal ultrasonograms, and cephalometric X-rays (used to evaluate facial bone growth). Although some evaluations were initiated while some patients were already on trial, they are informative in final analysis. Laboratory and clinical assessments were done more extensively and consistently in the early stages of the clinical trials.<sup>176</sup> The applicant acknowledges that some limitations apply to the datasets:

Special safety studies to monitor for acromegaly or other safety concerns including dental imprints, mandibular cephalometric x-rays, ring sizing, spleen and kidney ultrasounds, audiograms, tympanometry, and echocardiograms were sometimes difficult to interpret due to the lack of established standards for many of the tests in very small children. The interpretation of the measures was further complicated by the fact that many of the procedures were not implemented until most subjects had completed 2 to 3 years of treatment, so baseline evaluations were not available for comparison. The data from these tests, when baseline evaluations were not available, were used to complement information gathered from physical examinations and report of adverse events.

Additional clinical information has been presented in non-primary IGFD patient populations treated with mecasermin (Type 1 diabetes, Type 2 diabetes, HIV, healthy volunteers, as well as other conditions in several investigator-sponsored studies). Evaluation of other routes of administration (e.g. intravenous) has provided important safety information. Specifically, the observation that intravenous mecasermin administration was associated with syncope has led to complete avoidance of this route of administration in subsequent studies.

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<sup>176</sup> Safety assessments were not done uniformly across all mecasermin clinical studies. Early studies collected safety data more rigorously. Later studies (e.g. the investigator-sponsored Study 1419) focused on specific, protocol-defined adverse events.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Mecasermin is rhIGF-I. The physiology of IGF-I is well characterized and relatively well understood. In blood, IGF-1 is bound to six IGF binding proteins (> 80% of IGF-I is bound as a complex with IGFBP-3 and an acid-labile subunit). IGF-I is metabolized in the liver and kidneys; the latter appear to be the major clearance site in animal studies. The applicant did not conduct any formal human mecasermin metabolic studies.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Refer to section 7.2.5

#### 7.2.8 Assessment of Quality and Completeness of Data

Refer to Section 7.2.5 and 7.23. Hypoglycemia and adverse events already known to occur in association with GH (e.g. pseudotumor cerebri, arthralgia, myalgia) were anticipated on the basis of the known mechanism of action of IGF-I. They were appropriately evaluated in the clinical trials and generated information that can be labeled effectively. Several adverse events and laboratory findings, such as echocardiographic findings and liver enzyme elevations, were unexpected; although in general mild, they should be labeled as such.

#### 7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update includes information for the following studies: Study 1419,<sup>177</sup> Study MS301 (an ongoing open-label, randomized, multicenter, parallel-dose statural study of subjects with Primary IGFD), Study MS302 (a single-dose PK study of healthy subjects and subjects with IGFD), and Study MS302a (a multi-dose PK study of healthy subjects and subjects with IGFD). The safety update added 47 patient-years to the total exposure in primary IGFD in study 1419. SAEs are presented and discussed in sections

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<sup>177</sup> Five additional subjects have been enrolled in study 1419 since the last data cutoff date (31 December 2003) bringing the total of patients enrolled to 76 as of 07 April 2005.

7.1.1 and 7.1.2 The incidence of adverse events of “special interest” is presented in applicant’s Table 1.2-1. With the exception of hypoglycemia incidence, which increased from 42% to 49% as the exposure increased, the incidence for most adverse events of “special interest” changed minimally.<sup>178</sup>

**Table 1.2-1: Incidence of Adverse Events of Special Interest—Study 1419**

	Reported in NDA <sup>a</sup>	Subjects with New Visits <sup>b</sup>	Total <sup>c</sup>
<b>Total Subjects Enrolled</b>	<b>71</b>	<b>50</b>	<b>76</b>
Hypoglycemia	30 (42%)	8 (16%)	37 (49%)
Snoring	17 (24%)	0 (0%)	17 (22%)
Hypoacusis	16 (23%)	1 (2%)	17 (22%)
Tonsillar hypertrophy	11 (15%)	2 (4%)	13 (17%)
Middle ear effusions	8 (11%)	2 (4%)	10 (13%)
PE tube placement	10 (14%)	2 (4%)	12 (16%)
Tonsillectomy/adenoidectomy	7 (10%)	2 (4%)	8 (11%)
Intracranial hypertension	3 (4%)	0 (0%)	3 (4%)
Lipohypertrophy	21 (30%)	3 (6%)	24 (32%)
Arthralgia	7 (10%)	1 (2%)	8 (11%)
Myalgia	2 (3%)	0 (0%)	2 (3%)
Sleep apnea	3 (4%)	1 (2%)	3 (4%)

<sup>a</sup> The data cutoff date for NDA was 31 December 2003.

<sup>b</sup> Subjects for whom data were received between 31 December 2003 and 07 April 2005.

<sup>c</sup> Data cutoff date is 07 April 2005.

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The updated incidences of AEs in study 1419 are presented (by organ system) in applicant’s Table 1.2-2. The overall incidence of adverse events increased from 68% to 79 % (12 of the newly enrolled or continuing subjects reported an AE). The incidence increased by 4 percentage points for the “metabolism and nutritional disorders” AEs (49% in the original NDA and 53% in the 120-day safety update),<sup>179</sup> and by 3

<sup>178</sup> In addition, the applicant states that there were no reports of edema, myalgia, tumors, organomegaly, retinopathy during the safety update period. Arthralgia was reported in one subject (2%). Middle ear effusions were reported in two subjects (4%), otorrhea in one subject (2%), and hypoacusis in one subject (2%).

<sup>179</sup> Accounted by hypoglycemia in 8 patients.

percentage points for the “respiratory, thoracic, and mediastinal disorders” group (39% vs. 42 %),<sup>180</sup> “infections and infestations” (39% vs. 42 %),<sup>181</sup> and “reproductive and breast disorders” (10% vs. 13%).<sup>182</sup> For most of the other organ systems the incidences

**Table 1.2-2: Adverse Events by System Organ Class—Study 1419**

	Reported in NDA <sup>a</sup>	Subjects with New Visits <sup>b</sup>	Total <sup>c</sup>
<b>Total Subjects</b>	<b>71</b>	<b>50</b>	<b>76</b>
<b>Subjects Reporting at Least One Adverse Event</b>	<b>48 (68%)</b>	<b>30 (60%)</b>	<b>60 (79%)</b>
Metabolism and nutritional disorders	35 (49%)	8 (16%)	40 (53%)
General disorders and administration site conditions	29 (41%)	7 (14%)	32 (42%)
Respiratory, thoracic, and mediastinal disorders	28 (39%)	8 (16%)	32 (42%)
Infections and infestations	28 (39%)	8 (16%)	32 (42%)
Nervous system disorders	26 (37%)	5 (10%)	28 (37%)
Gastrointestinal disorders	23 (32%)	4 (8%)	25 (33%)
Ear and labyrinth disorders	21 (30%)	2 (4%)	23 (30%)
Musculoskeletal and connective tissue disorders	21 (30%)	3 (6%)	23 (30%)
Investigations	21 (30%)	4 (8%)	23 (30%)
Skin and subcutaneous tissue disorders	17 (24%)	3 (6%)	19 (25%)
Blood and lymphatic system disorders	16 (23%)	0 (0%)	16 (21%)
Surgical and medical procedures	12 (17%)	0 (0%)	12 (16%)
Eye disorders	12 (17%)	1 (2%)	13 (17%)
Injury, poisoning, and procedural complications	10 (14%)	1 (2%)	11 (14%)
Cardiac disorders	9 (13%)	1 (2%)	9 (12%)
Congenital, familial, and genetic disorders	8 (11%)	1 (2%)	9 (12%)
Psychiatric disorders	8 (11%)	0 (0%)	8 (11%)
Renal and urinary disorders	8 (11%)	0 (0%)	8 (11%)
Reproductive and breast disorders	7 (10%)	3 (6%)	10 (13%)
Neoplasms: benign, malignant, and unspecified	1 (1%) <sup>d</sup>	0 (0%)	1 (1%) <sup>d</sup>
Endocrine disorders	1 (1%)	1 (2%)	2 (3%)
Hepatobiliary disorders	1 (1%)	0 (0%)	1 (1%)
Social circumstances	1 (1%)	0 (0%)	1 (1%)
Vascular disorders	1 (1%)	0 (0%)	1 (1%)

<sup>a</sup> The data cutoff date for NDA 21-839 was 31 December 2003 (NDA 21-839, Section 5.3.5.2.4, Table 13.2.1-1).

<sup>b</sup> Subjects for whom data were received between 31 December 2003 and 07 April 2005.

<sup>c</sup> Data cutoff date is 07 April 2005, includes 5 new subjects.

<sup>d</sup> Wants on toe.

did not change.

<sup>180</sup> Accounted by adenoidal hypertrophy (2 patients), cough (4 patients), “nasal turbinate hypertrophy” (1 patient), postnasal drip (1 patient), and tonsillar hypertrophy (2 patients).

<sup>181</sup> Accounted primarily by standard childhood infections (it included also an injection site abscess).

<sup>182</sup> Accounted by “breast pain,” gynecomastia and ovarian cyst (one patient each).

As noted in the original NDA, several out-of-range observations in baseline laboratory evaluations were commonly seen in IGF1 subjects and included: decreased hemoglobin, decreased hematocrit, increased cholesterol, eosinophilia, and, to a lesser extent, increased triglycerides. The applicant states that “no new type of laboratory abnormality has been seen in new subjects.”

Changes in liver function tests were occasionally seen in studies MS302 and MS302a and are summarized in applicant’s Table 1.3-2. Two subjects in Study MS302a reported increases in SGOT and SGPT that were  $\geq 2X$  over baseline values and returned to normal within 30 days of treatment cessation. A third patient (302-2012) also had increases in SGOT and SGPT that were  $\geq 2$  times above baseline but did not return for the requested post-study visit. Five additional subjects are reported to have had increases in transaminases to values above age-related norms, but these increases were deemed clinically insignificant.<sup>183</sup>

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<sup>183</sup> This reviewer’s analysis of the MS302 (XLAB) dataset reveals that there were 4 SGPT values above normal in two patients; patient 2012 had an increased SGPT at screening (54.5) and at follow-up (131.1 or 3.1 X ULN); patient 1007 had a screening SGPT slightly above the upper limit of normal of 42 (46.6) and normal at follow-up. A review of the MS302a (XLAB) dataset identified 6 above-normal values in 5 patients: patient 4010 had a minimally elevated SGPT at “PK Phase” time (35.1 with upper limit of normal of 31 IU); patient 4013 had an elevated SGPT value at screening (55.2 with upper limit of normal of 31 IU) and at “PK phase” (209 or 6.7 X ULN); patients 5005, 5009 and 5012 had elevated SGPTs at the “PK phase” of 60.7, 4.4 and 88.6, respectively (upper limit of normal 41 IU); of the latter group only patient 5012 had an elevation  $> 2X$  ULN (2.2 X). The applicant does not specify if these subjects were adult volunteer or patients with primary IGF1.

Table 1.3-2: Subjects with Abnormal Transaminase Values

Subject	Time	SGOT (IU/L)	SGPT (IU/L)	Total Bilirubin (mg/dL)
302a-5012	pre-dose	18.8	11.5	0.8
	post-dose	77.3 <sup>a</sup>	88.6 <sup>a</sup>	1.0
	follow-up <sup>b</sup>	26.2	14.1	1.0
302a-4013	pre-dose	41.2 <sup>a</sup>	55.2 <sup>a</sup>	0.9
	post-dose	99.5 <sup>a</sup>	209.6 <sup>a</sup>	0.8
	follow-up <sup>b</sup>	22.5	19.8	0.4
302a-5004	pre-dose	35.4	28.6	0.5
	post-dose	39.7 <sup>a</sup>	35.8	0.6
	follow-up	ND	ND	ND
302a-5005	pre-dose	26.4	22.7	0.5
	post-dose	42.7 <sup>a</sup>	60.7 <sup>a</sup>	0.4
	follow-up <sup>b</sup>	ND	ND	ND
302a-5009	pre-dose	18.8	26.6	0.7
	post-dose	24.3	44.4 <sup>a</sup>	1.0
	follow-up <sup>b</sup>	ND	ND	ND
302a-4010	pre-dose	20.3	22.1	0.6
	post-dose	27.2	35.1 <sup>a</sup>	0.7
	follow-up <sup>b</sup>	ND	ND	ND
302-2012	pre-dose	30.5	54.5 <sup>a</sup>	0.7
	post-dose	244.6 <sup>a</sup>	131.1 <sup>a</sup>	0.7
	follow-up	ND	ND	ND
302-3002	pre-dose	20.8	24.4	1.2 <sup>a</sup>
	post-dose	60.6 <sup>a</sup>	23.7	0.5
	follow-up	ND	ND	ND

ND, not done.

<sup>a</sup> Laboratory value is above the normal range.

<sup>b</sup> Follow-up values were collected after database lock. Details of follow-up values can be found in individual subject files.

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At the cut-off date of 07 April 2005, in Study 1419, 3/34 (9 %) subjects are reported to have had elevated BUN, 17/34 (50 %) had elevated cholesterol, and 11/33 (33 %) had elevated triglycerides when last evaluated; the applicant points out that “these rates were similar to the corresponding rates reported in the original NDA [4/34 (12%), 17/34 (50%), and 9/31 (29%), respectively].

In conclusion the safety findings of the 120-day safety update are consistent with the observations made from the original NDA datasets and did not identify any new safety concerns.

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

It is important to recognize from the beginning that there is no comparator group against which the incidence of adverse events collected in the primary IGFD clinical program can be evaluated.<sup>184</sup> In addition, Laron Syndrome itself is not simply a condition of severe short stature; it has a complex physical and metabolic picture with multiple biochemical and structural abnormalities, some of which may not be fully understood or characterized. Finally, the mecasermin primary IGFD clinical program is relatively heterogeneous with respect to the safety variables evaluated, as the frequency and the type of safety assessments differed to some extent between studies and even within the same study. Therefore, in drawing final safety conclusions one has to rely on a combination of observations including of the frequency and severity the safety findings, the information already available from the use of GH for other indications (since IGF-I is GH's major mediator and the clinical experience with GH is extensive) and to a lesser extent the placebo-controlled mecasermin clinical trials conducted in pediatric patients for other indications investigational. Final conclusions (and corresponding recommendations for labeling) follow:

- Hypoglycemia in general and hypoglycemic seizures in particular can accompany mecasermin treatment. Their occurrence and severity can be reduced or mitigated by (1) careful titration of mecasermin at treatment initiation (accompanied by frequent glucose monitoring), (2) dietary advice to ensure appropriate food ingestion when mecasermin is administered, (3) availability of an emergency glucose source and/or glucagon pen, and (4) avoidance of high risk activities for older children within 2-3 hours after mecasermin injection. Consideration should be given to instructing patients at treatment initiation in a manner similar to that done for insulin.
- Lymphoid tissue hypertrophy associated with symptoms such as tonsillar enlargement, snoring, chronic middle ear effusions, sleep apnea, and need for tonsillectomy/adenoidectomy appears to occur in association with mecasermin treatment. Such adverse events can be easily monitored clinically and appropriate corrective interventions, if and when necessary, are available and common in pediatric practice.
- Adverse events similar to those described for GH treatment have been observed (e.g. arthralgia, myalgia, and papilledema). It is likely that in a larger patient population and with additional patient exposures to mecasermin additional GH-related (and IGF-I mediated) adverse events may be observed in the future. Therefore, it appears prudent to mention this class of adverse events in the mecasermin label.
- Injection site reactions are frequent and should be explicitly described in the label along with strategies to minimize their occurrence (injection site rotation).
- Although evidence of organomegaly has not been clearly seen, kidney and splenic lengths occasionally surpassed the 90th and the 95th percentile, respectively.
- Facial changes (coarsening and overgrowth of the facial soft tissues, thickening of the nasal lip and mucosa, faster mandibular growth relative to other facial bones), although not studied

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<sup>184</sup> In essence, the primary IGFD clinical program included single- and multicenter, baseline-controlled, open-label clinical trials.

extensively, appear to occur in association with mecasermin treatment and should be mentioned in the label.

- A causal relationship between cardiac echocardiographic findings and mecasermin treatment cannot be made with certainty.
- Although there is no a priori reason to expect liver enzyme elevation in association with IGF-I (and mecasermin) replacement therapy, several patients had ALT elevations on trial; until this phenomenon is better characterized by additional clinical data, the drug label should include this information and patients should be monitored for LFT elevations.
- Clinical laboratory abnormalities in serum cholesterol, triglycerides, LDH, and AST occurred during the clinical trials; whether they are disease specific (likely) and in some patients treatment-specific, it cannot be ascertained without a control group. These findings should be labeled so that practitioners treating these patients will evaluate them in clinical practice.
- Finally, since IGF-I is an anabolic hormone very close functionally to GH, the potential risk for abuse in the marketplace needs to be acknowledged.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

Due to the rarity of primary IGFD, the small size of some of the individual clinical studies (some included as few as 6-8 patients), and the relative homogeneity of the condition, the efficacy and safety datasets were pooled across all clinical studies for an integrated analysis of efficacy and safety.

#### 7.4.1.2 Combining data

Refer to Section 7.4.1.1. above.

### 7.4.2 Explorations for Predictive Factors

#### 7.4.2.1 Explorations for dose dependency for adverse findings

The number of adverse events that were drug-related was too small to allow any further exploratory analyses. One exception is hypoglycemia, which occurred in a time-dependent

manner (it had a higher incidence at the beginning of the treatment, particularly during the first month when 18 % of all hypoglycemic episodes took place). There was no dose-dependency for hypoglycemia as indicated by the fact that the few episodes characterized as severe occurred across both doses studied.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Refer to Section 7.4.2.1.

#### 7.4.2.3 Explorations for drug-demographic interactions

Refer to Section 7.4.2.1.

#### 7.4.2.4 Explorations for drug-disease interactions

Refer to Section 7.4.2.1.

#### 7.4.2.5 Explorations for drug-drug interactions

Refer to Section 7.4.2.1.

### 7.4.3 Causality Determination

Assigning adverse event causality is particularly difficult in the absence of a control group. Several AEs, however, could be linked to mecaseermin on the basis of the known insulin-like effect of IGF-I (hypoglycemia), its proliferative effect (tonsillar hypertrophy, sleep apnea, snoring, organomegaly), or the known adverse event profile of GH (arthralgia, myalgia, pseudotumor cerebri).

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The mecaseermin dosing regimen proposed in the label (80-120 µg/kg BID) is supported by data presented in this NDA and is fully consistent with data published in the medical literature. (Refer to Section 8.6: Literature Review). The applicant not only has established an effective dose-regimen with respect to enhancing linear growth but has also characterized a minimally effective dose and a dose response for mecaseermin in patients with primary IGF1D. In addition, data from the pharmacokinetic studies and on-

trial IGF-I measurements following mecasermin administration indicate that the 120 µg/kg dose raises the serum IGF-I concentrations within the normal range for a few hours in patients with severe primary IGFD.

### Minimally effective dose

In Study F0632 (a small Phase III open-label, baseline-controlled study conducted in treatment-naïve patients with growth hormone insensitivity syndrome) six patients received 60 µg/kg BID of mecasermin for one year. The mean  $\pm$ SD height velocity at Month 12 was  $5.4 \pm 2.3$  cm/yr, in excess of the baseline height velocity of  $1.2 \pm 0.6$  cm/yr but below that observed with the to-be-marketed regimen of 80-120 µg/kg BID, which was  $8.0 \pm 2.2$  cm. In addition, the mean change in height velocity relative to baseline for the 60 µg/kg BID regimen (4.1 cm)<sup>185</sup> was inferior to the to-be-marketed regimen ( $5.2 \pm 2.6$  cm) and was not associated with significant changes in height SDS.<sup>186</sup>

### Dose response

An analysis that compares the mean height velocity obtained with the 120 µg/kg BID dose versus that obtained with  $\leq 80$  µg/kg BID indicates a statistically significant difference for Year 1 and Year 2 of treatment ( $p=0.0003$  and  $p = 0.0265$ , respectively).<sup>187</sup> The individual responses to mecasermin (height velocity at one year)

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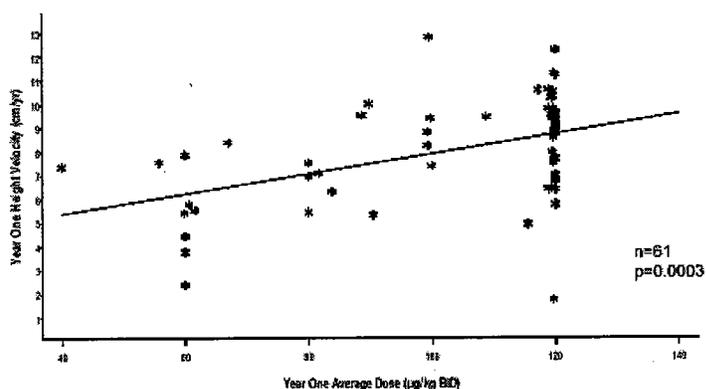
<sup>185</sup> Individual changes were: 1.4 cm, 2.6 cm, 5.9 cm, 2.8 cm, 4.4 cm and 7.9 cm respectively.

<sup>186</sup> Height SDS was  $-7.8 \pm 2.0$  at baseline and  $-7.9 \pm 2.1$  at Month 12; thus, the mean height SDS change for the 60 µg/kg BID regimen was 0.1 during the first year of treatment. In contrast, for the same length of time the change in height SDS for the to-be-marketed regime was  $0.8 \pm 0.5$ .

<sup>187</sup> A similar comparison conducted for the third year of treatment was not presented; the applicant comments that "beginning with year 3, there were few subjects treated at 80 µg/kg BID or less making it difficult to establish a dose-related effect of treatment."

are presented for the in 61 patients who contributed data to the primary efficacy analysis of Study 1419 (applicant's Figure 11.8-1). Making allowances for some variability in individual responses at each particular dose, subjects receiving higher doses (120 µg/kg BID) had better responses than subjects receiving lower doses (60µg/kg BID).

Figure 11.8-1: Year One Height Velocity Versus Year One Average Dose (Subjects Naïve To Mecasermin)



## 8.2 Drug-Drug Interactions

The applicant states that “no in vitro or in vivo drug interaction studies were conducted for mecasermin.”

## 8.3 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, race<sup>188</sup> or co-morbid states (such as renal or hepatic failure) on mecasermin efficacy and safety. However,

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<sup>188</sup> In the efficacy population 48 (79%) patients were Caucasian, 3 (5%) were African American, 6 (10%) were Hispanic, 3 (5%) were Asian, and 1 (2%) were in the “Other” category.

several observations were made in analyses of various subgroups of patients. There was no correlation between age and year one height velocity (n=61, p=0.52). Safety information accumulated during the primary IGFD clinical trials suggests that younger children may be at higher risk for hypoglycemia. There was no apparent gender-effect. An efficacy analysis comparing the mean difference in Year One height velocity between males (n=37) and females (n=24) did not identify significant differences between the two groups (t-test p=0.39). The applicant also states that a "review of adverse events reported during treatment did not show any differences in the type or frequency of adverse events between male and female subjects."

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#### **8.4 Pediatrics**

Mecasermin is intended exclusively for the treatment of short stature in pediatric patients with primary IGFD. A pediatric waiver should be granted for children less than 2 years of age.

#### **8.5 Advisory Committee Meeting**

There were no Advisory Committee Meetings for this application.

#### **8.6 Literature Review**

Several clinical studies of rhIGF-1 use in patients with GH receptor deficiency (Laron type) have been published in the medical literature in the last two decades. They are summarized next. They include mostly short-term data (i.e.  $\leq 3$  years). Some small series include patients followed up long-term (up to 6-7 years).

##### **Short-term studies**

**1) Ranke MB et al.: Insulin-like growth factor I improves height in growth hormone insensitivity: two years results (Horm Res 1995; 44: 253-264).**

This study (a baseline-controlled series) included 31 patients with growth hormone insensitivity syndrome (GHIS) and two patients with GH gene deletion<sup>189</sup> who were treated with 40-120 µg/kg twice daily for two years. Patient baseline characteristics (mean values) are provided for chronological age (10.9 years; range 3.7 to 19.6), bone age (7.7 years; range 1.8 to 13.3), and height SDS (-6.8 ± 1.6). At the end of 1-year of rhIGF-1 treatment of 26 patients, height velocity (HV) more than doubled<sup>190</sup> and height SDS increased by 0.8 ± 0.5. After two years of treatment in 18 patients, height velocity was still higher than it was at baseline (but slowed down relative to that observed after one year<sup>191</sup>) and height SDS further increased by 0.4. There was no undue progression of bone age: mean bone age advancement was 1.2 years during the first year and 1.5 during the second year, respectively, as patients started with a delayed mean bone age of approximately 2.2 years relative to chronological age. Puberty progression (pubertal signs and testicular volume) “did not progress faster than in the normal population.” The most common adverse events were headache (21 events), early hypoglycemia (13), reversible papilledema (1), reversible Bell’s palsy (1), late lipohypertrophy (7), and late tonsillectomy/adenoidectomy (3).

## **2) Kinger B and Laron Z: Three year IGF-I treatment of children with Laron syndrome (Journal of Pediatric Endocrinology and Metabolism, 8, 149-158, 1995)**

This study was also a baseline-controlled series. It included nine prepubertal children with Laron syndrome aged 0.5 to 14.6 years who were treated with daily IGF-1 injections of 150-200 µg/kg. Mean baseline characteristics were as follow: chronological age of 7.4 ± 1.7 years, bone age of 5.1 ± 1.5 years, height SDS of -5.7 ± 3.9 years. All nine patients completed one year of treatment, six completed two years and five completed three years. Height velocity increased from 4.6 ± 1.3 cm/yr at baseline to 8.2 ± 0.8 cm/yr after 1-year (p < 0.0001), 6.0 ± 1.3 cm/yr after 2 years ((p < 0.004), and 4.8 cm/yr after 3 years of treatment, respectively. Mean height SDS changed from -5.6 ± 1.5 at baseline to -5.2 ± 1.7 at one year, -5.8 ± 1.2 at two years, -5.5 ± 1.2 after three years. Bone maturation was not excessive relative chronological age advancement.<sup>192</sup> Limited safety data are presented. The authors state that “the drug was well tolerated, without major undesirable effects.”

## **3) Guevara-Aguire J et al.: A randomized, double blind, placebo-controlled trial on safety and efficacy of recombinant human insulin-like growth factor-I in children with growth hormone receptor deficiency (J Clin Endocrinol Metab 80: 1393-1398, 1995).**

This small study was the only of placebo controlled study of IGF-I in patients with GHRD. Seventeen prepubertal patients from Ecuador were randomized to either rhIGF-I (120 µg/kg BID, 7 patients) or placebo (9 patients). After 6 months, the placebo treated patients were

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<sup>189</sup> Patients with GH gene deletion cannot be treated with GH because they recognize the GH molecule as a foreign protein.

<sup>190</sup> It increased from 3.9 ± 1.8 cm to 8.5 ± 2.1 cm.

<sup>191</sup> 6.4 ± 2.2 cm after 2 years vs. 8.6 ± 1.7 cm after one year for the 18-patient cohort.

<sup>192</sup> Mean chronological age/bone age ratio was 1.8 ± 0.7 at baseline, 1.6 ± 0.4 at one year, 1.7 ± 0.5 at 2 years, and 1.4 ± 0.3 at 3 years.

switched to IGF-I. Subjects receiving rhIGF-I increased their height velocity at 6 months from a pretreatment rate of  $2.9 \pm 0.6$  to  $8.8 \pm 0.6$  cm/yr ( $p < 0.05$ ).<sup>193</sup> In contrast, placebo-treated patients had only a modest, not-statistically significant improvement in height velocity from  $2.8 \pm 0.3$  cm/yr to  $4.4 \pm 0.7$  cm/yr ( $p > 0.05$ ).<sup>194</sup> When switched to rhIGF-I for the next 6 months of treatment, placebo treated patients improved their annualized height velocity to  $8.7 \pm 0.6$  cm/yr (almost identical to the height velocity of IGF-1 treated cohort for the first 6 months). The publication does not provide a statistical comparison between the placebo and IGF-1 treatment groups for the first 6-months of treatment. From a safety standpoint, the study reports one case of papilledema (bilateral, reversed within 6 days) observed one month after initiation of therapy. The number of hypoglycemic events was identical (6) between the two treatment groups (the incidence, however was not reported).<sup>195</sup> There were two events of transient elevation of liver enzyme in the IGF-I cohort but the incidence data was not reported.

#### **4) Guevara-Aguire J et al.: Two-year treatment of growth hormone (GH) receptor deficiency with recombinant insulin-like growth factor I in 22 children: comparison of two dosage levels and GH-treated GH deficiency (J Clin Endocrinol Metab 82: 629-633, 1997).**

This case-series includes patients previously described in the previous reference and additional data up to two years of treatment. It includes 22 patients treated with either 120  $\mu\text{g}/\text{kg}$  BID ( $n=15$ ) or 80  $\mu\text{g}/\text{kg}$  BID ( $n=7$ ) of IGF-1 for up to three years. The baseline patient characteristics for the “120  $\mu\text{g}/\text{kg}$ ” cohort were as follows: chronological age of  $9.8 \pm 3.4$  years, bone age of  $4.9 \pm 2.0$  years, height velocity of  $3.4 \pm 1.4$  cm/yr, height SDS of  $-8.5 \pm 1.3$ . These baseline characteristics were very similar to those of the “80  $\mu\text{g}/\text{kg}$ ” cohort: chronological age of  $7.6 \pm 4.7$  years, bone age of  $4.0 \pm 3.5$  years, height velocity of  $3.0 \pm 1.8$  cm/yr, height SDS of  $-8. \pm 1.8$ . Both doses of IGF-1 improved height velocity for up to 3 years<sup>196</sup> and height by approximately 0.9 at one year and an additional 0.5 at two years.<sup>197</sup> When these changes were compared to those induced by GH treatment in GH-deficient individuals, the magnitude of the IGF-1 response in patients with GHRD was less than that reported with GH in GHD.<sup>198</sup> This is

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<sup>193</sup> For the whole first year of treatment the height velocity was  $8.6 \pm 0.4$  cm/yr (the 6-12 months height velocity was  $8.4 \pm 0.7$  cm/yr).

<sup>194</sup> This increase in height velocity was ascribed by the authors to improved nutrition during the clinical trial.

<sup>195</sup> Patients with Laron syndrome have an increased incidence of hypoglycemia, presumably due to the absence of GH action as a counterregulatory hormone. IGF-1 treatment has itself a hypoglycemic action since IGH-1 has 6-10% of the hypoglycemic activity of insulin.

<sup>196</sup> For the “120  $\mu\text{g}/\text{kg}$  cohort” height velocity improved from  $3.4 \pm 1.4$  cm/yr at baseline to  $8.8 \pm 1.1$  cm/yr at one year,  $6.4 \pm 1.1$  cm/yr at 2 years, and  $5.7 \pm 1.4$  cm/yr at 3 years. For the “80  $\mu\text{g}/\text{kg}$  cohort” height velocity improved from  $3.0 \pm 1.8$  cm/yr at baseline to  $9.1 \pm 2.2$  cm/yr at one year, and  $5.6 \pm 2.1$  cm/yr at 2 years.

<sup>197</sup> For the “120  $\mu\text{g}/\text{kg}$  cohort” height SDS improved by  $1.0 \pm 0.4$  at 1 year and an additional  $0.5 \pm 0.3$  at two years. For the “80  $\mu\text{g}/\text{kg}$  cohort” height SDS improved by  $0.8 \pm 0.2$  at 1 year and an additional  $0.5 \pm 0.3$  at two years.

<sup>198</sup> For instance, height velocity change from baseline in response to IGF-1 (across dose groups) in the current study was  $5.5 \pm 1.4$  at one year,  $2.9 \pm 1.6$  at two years, and  $2.9 \pm 1.2$  at three years. For comparison, the height velocity changes in a cohort of 11 GHD children treated with GH were  $8.8 \pm 2.5$  at one year,  $6.1 \pm 3.1$  at two years, and  $6.5 \pm 2.4$  at three years. The change in height SDS at two years was  $1.4 \pm 0.6$  and  $2.2 \pm 1.0$  in response to IGF-1 and GH, respectively.

consistent with the observation that approximately 20% of GH-influenced growth is the result of direct effects of GH on bone.

**5) Backeljaw P F, et al.: Prolonged treatment with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome - a clinical research center study (J Clin Endocrinol Metab 81: 3312-3317, 1996).**

This case-series includes eight children with GHIS (five with GHRD and three with growth-attenuating antibodies to GH) who were treated with rhIGF-I for 2 years (dose range of 80-120 µg/kg BID). Baseline mean height SDS was -5.6 (range -3.4 to -7.0) and baseline mean height velocity was 4.0 cm/yr (equivalent to a -2.4 SD score). During the first year of therapy the mean HV increased 2.4-fold to 9.3 cm/yr (+3.6 SD score); during the third year it was 6.2 cm/yr (+0.5 SD score). The average change in height SDS after 2 years of treatment was +1.2 (range 2.1 to -0.3). Adverse events reported included lipohypertrophy at injection sites, mild thickening of the soft tissues of the nose and eyebrows (in two of the oldest patients), transient increase in intracranial pressure with papilledema) during the first month of therapy which resolved spontaneously in 2-3 weeks despite continuation of IGF-I therapy, asymptomatic decreased serum potassium concentrations (as low as 2.4 mmol/L) which recovered spontaneously within 1-2 hours.

The authors studied the effect of rhIGF-I treatment on several laboratory tests (including glucose and lipids), on bone mineral density, and on the growth of several organs (including spleen, heart, and kidneys). These results can be summarized as follows:

- Bone mineral density of the lumbar spine (presented descriptively in 8 patients) appear to increase on therapy relative to baseline (uncontrolled data).
- Spleen growth (below the 10<sup>th</sup> percentile for age in 7 out of 8 patients at baseline) was dramatically accelerated particularly during the first year of treatment; during 2<sup>nd</sup> and 3<sup>rd</sup> years of study the spleen growth was within normal age-related standards except for two patients who experienced rapid growth (90<sup>th</sup> percentile).
- Most patients had an apparent increase in their nasopharyngeal lymphoid tissue and developed snoring during sleep. One patient developed sleep apnea and required tonsillectomy/adenoidectomy after one year of therapy. Another patient developed tonsillar hypertrophy that causes intermittent discomfort when swallowing solid foods.
- Kidney length increased rapidly on therapy. At baseline, kidney length was below the 50<sup>th</sup> percentile for height and below the 5<sup>th</sup> percentile for age in seven out of eight patients. On treatment, six patients had renal lengths above the 75<sup>th</sup> percentile for height and four were at or above the 95<sup>th</sup> percentile.
- Cardiac echocardiograms performed in each patient after 2 (or 3) years of treatment revealed “normal intracardiac anatomy and ventricular function.”
- There were “no consistent effects of IGF-I therapy on white blood cell count, erythroid indexes, platelets, reticulocytes, total serum protein, albumin, calcium, phosphorus, bilirubin, lactate dehydrogenase, uric acid, AST, ALT, serum electrolytes, T4, or TSH.
- Occasional hypoglycemia was noted in some patients and was managed by reducing the doses of IGF-1.

- Mean urinary calcium/creatinine ratio increased on treatment; the individual response was variable with some individual patients showing no change on treatment, while others having 7-6-fold increases.

## Long-term studies

### 1) Backeljaw PE et al.: Therapy for 6.5-7.5 years with recombinant insulin-like growth factor I in children with growth hormone insensitivity syndrome: a clinical research center study (J Clin Endocrinol Metab 86: 1504-1510, 2001).

This is a case-series of eight patients who were treated with IGF-I at doses of 80-120 µg/kg/BID for 6.5 to 7.5 years. It extends information on a group of patients previously reported (see above-summarized study). Height velocity improved on treatment from 4 cm/yr at baseline to 9.3 cm/yr for the first year and 6.2 cm/yr for the second year. Height velocity for years 3-6 was 5.4, 5.5, 5.2, and 4.8 cm/yr respectively. Height velocity SD score improved from -2.4 at baseline to -0.8, -0.8, and -0.4 during years 3-6 of treatment, respectively (there was large variability between patients with a range of -1.8 to +6.6). The mean height SD score improved from -5.6 at baseline to -4.5, -4.4, and -4.2 after 2, 4, and 6 years of therapy, respectively. The mean change in height SD score after 6-7 years of therapy was +1.4 (range -1.2 to 4.0). In general, skeletal age increased proportional to chronological age before puberty. For patients entering puberty (n=4) skeletal maturation was faster (mean CA/BA ratio was 1.4). Spleen growth, which was particularly rapid during the first 1-2 years of treatment, progressed at a 'normalized' pace. A second patient developed obstructive sleep apnea and required a tonsillectomy after 4 years of therapy. Kidney growth increased rapidly during the first 4 years of therapy (5 of 8 patients achieved a renal growth at or above the 95<sup>th</sup> percentile). At 6-7 years of treatment renal growth was above the 95<sup>th</sup> percentile in six out of eight evaluated patients. There were no structural abnormalities observed on ultrasounds. The authors report that "creatinine clearance was normal after 4-5 yr of treatment (87-120 mL/min/1.73 m<sup>2</sup>. And did not change significantly thereafter." In some patients IFG-1 therapy was associated with "overgrowth of the soft tissues of the face leading to a prominent glabella and thickening of the eyebrows, nasal tip, philtrum, and lips;" such changes were more prominent in patients experiencing puberty. In one patient who was observed for 14 months after IGF-1 treatment was discontinued, "considerable reduction of the soft tissues overgrowth was noted." The observations made for laboratory analytes were similar after 3-6 years to those noted and reported previously (see above-summarized study). Five of eight patients had "borderline-high or high cholesterol concentrations (range 5.0-5.9 mmol/L.)" Lipohypertrophy at the injection site (which resolved when the injections were "dispensed properly") and hypoglycemia ("more frequent and more pronounced in younger children early in treatment," including a "brief hypoglycemic seizure") were the only adverse events reported.

### 2) Ranke MB et al.: Long-term treatment of growth hormone insensitivity syndrome with IGF-I. Results of the European Multicenter Study (Horm Res 1999; 51: 128-134).

This multicenter (22 centers from 12 countries), European baseline-controlled study enrolled 33 patients (31 had Laron syndrome and 2 had congenital GH gene deletion). The IGF-1 dose was

40-120 µg/kg BID. Seventeen patients were treated for 4 years or longer (including six patients treated for up to 6 years). Mean chronological age at the beginning of treatment for this cohort was 9.1 years (range 3.7-13.5); their mean height SD score at baseline was  $-4.9 \pm 1.3$ . At the end of the observation period the mean age for these 17 patients was 14.2 (range 9.1-17.7) and the mean height SD score was  $-4.9 \pm 1.9$ ; the height gain was  $1.7 \pm 1.2$  SDS. Two patients who started treatment before age 5, reached the 3<sup>rd</sup> percentile of the normal population during the final year of treatment. The overall height SDS gain correlated negatively with the age at the initiation of therapy (n=17,  $R^2=0.613$ ,  $p<0.001$ ). A limited number of observations suggest that the onset of puberty was not premature<sup>199</sup>. There were not enough observations to assess the duration of puberty. Contrary to some previous observations, a substantial gain in fat mass was observed in all but one patient. BMI was  $0.6 \pm 1.8$  SDS at start of the treatment and  $1.8 \pm 1.5$  SDS at the end (BMI SDS change =  $1.24 \pm 1.62$ ). Height SDS change correlated positively with the change in BMI SDS (n=17,  $R^2=0.348$ ,  $p<0.01$ ).

## 8.7 Postmarketing Risk Management Plan

The application does not include a postmarketing risk management plan.

## 8.8 Other Relevant Materials

The ODS consult has been reviewed. Its extensive recommendations have been incorporated in the patient package insert.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

Mecasermin treatment was effective in increasing linear growth in patients with severe primary IGFD at doses of 80-120 µg/kg BID. Mecasermin more than doubled the mean height velocity in the first year of treatment, induced a distinct “catch-up” growth phenomenon, maintained height velocities above those present at baseline, and improved mean height SDS. These changes were both statistically and clinically significant, particularly taking in consideration the extreme short stature of patients with primary IGFD and the disadvantages associated with it.

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<sup>199</sup> Onset of puberty was assessed as a breasts Tanner 2 in girls and testicular volume >3 ml in boys.

These observations along with some preliminary results that suggest a potentially substantial increase in final height (up to 20 cms) indicate that mecasermin is an effective drug product for the proposed indication. When judged in the context of linear growth with other products (specifically GH), the growth observed with mecasermin is slower than that observed in GH deficiency and comparable to that observed in idiopathic short stature during the first year of treatment. There are no differences between this reviewer's and the applicant's efficacy conclusions.

The adverse event profile of mecasermin, judged within the limits of a baseline-controlled clinical trial without a comparator cohort for the safety observations, is consistent with that published in the medical literature to date and confirms in general to IGF-I's known mechanisms of action (insulin-like activity and main mediator of GH's action). Several safety observations made in the clinical trial related to laboratory abnormalities (including liver enzyme elevations), ultrasonographic (including echocardiographic) findings do not have in general clear clinical correlates and cannot be differentiated from either background illnesses/adverse events or clinical features related to Laron Syndrome itself. In general there are no major differences between this reviewer's and applicant's safety conclusions.

Accepting the limitations of a baseline-controlled clinical trial and the fact that a placebo-control clinical trial is unethical and cannot be conducted in severe primary IGFD, and taking into consideration the extreme short stature observed in primary IGFD, mecasermin has an acceptable benefit-to-risk profile for the proposed indication if used according to the label.

## **9.2 Recommendation on Regulatory Action**

From a clinical perspective, mecasermin should be approved as replacement therapy for the orphan indication of severe short stature in (1) patients with primary IGF-I deficiency and (2) in

patients with growth hormone gene deletion and neutralizing antibodies to growth hormone (GH).

### **9.3 Recommendation on Postmarketing Actions**

#### **9.3.1 Risk Management Activity**

The applicant should propose a plan that addresses the potential off-label use of mecasermin as an anabolic agent.

#### **9.3.2 Required Phase 4 Commitments**

None.

#### **9.3.3 Other Phase 4 Requests**

None.

### **9.4 Labeling Review**

The applicant's proposed labeling is in general acceptable. Several changes are recommended by this reviewer and presented in the line-by-line labeling review, which includes the current labeling version that is being negotiated with the applicant. The recommended changes are:

- a more extensive description of inclusion criteria and baseline characteristics
- several clarifications in the Precautions section
- a recommendation to add a description of several laboratory and special assessment observations that were observed in the clinical trials
- a recommendation to expand and clarify the information that relates to the titration of Increlex at treatment initiation

### **9.5 Comments to Applicant**

See comment under the Risk management Activity Section.

14 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

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