

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-884**

**MEDICAL REVIEW(S)**

# MEDICAL OFFICER REVIEW

## Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #: 21-884

APPLICATION TYPE: Commercial

SPONSOR: Insmed Inc.

PROPRIETARY NAME: iPLEX

CATEGORY OF DRUG: Recombinant human insulin-like growth factor-1

USAN / Established Name: Mecasermin rinfabate

ROUTE: injectable

MEDICAL REVIEWER: Dragos Roman

REVIEW DATE: 11/15/05

### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
October 12, 2005		Complete Response to Approvable Letter	

### RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
September 20, 2005	NDA Clinical Review (21-884)	

### Executive Summary:

Mecasermin rinfabate (trade name: iPLEX) is recombinant human insulin-like growth factor-I (rhIGF-1) complexed non-covalently with recombinant human insulin-like growth factor binding protein-3 (rhIGFBP-3). Insmed Inc. submitted a New Drug Application for iPLEX on January 3, 2005 (NDA 21-884). The indication sought is treatment of short stature in children with growth hormone insensitivity syndrome (also called primary IGF-I deficiency). On September 26, 2005 the division issued an "Approvable Letter" listing multiple CMC deficiencies (there were no clinical approvability issues). On October 12, 2005 Insmed Inc. submitted a Complete Response to the September 26, 2005 Approvable Letter that includes, among others, a response to CMC deficiencies, revised labels (PI, PPI, vial and carton labels), and a clinical safety update. The clinical safety update contains a limited amount of new clinical data; it does not raise any new safety signals. The new proposed labeling (PI and PPI) is acceptable with minor modifications. In response to a request formulated in the Approvable Letter, Insmed agrees to continue to monitor post-approval the immunogenicity of iPLEX for a duration of 2 years (i.e. the duration of the on-going pivotal trial). Finally, and importantly, there are no changes in this reviewer's recommendation for iPLEX approval from a clinical perspective.

Outstanding Issues: None

### Recommended Regulatory Action:

New Clinical Studies: \_\_\_\_\_ Clinical Hold \_\_\_\_\_ Study May Proceed

NDA: Approval

Efficacy / Label Supp.: \_\_\_\_\_ Approvable \_\_\_\_\_ Not Approvable

Signed: \_\_\_\_\_ Medical Reviewer: \_\_\_\_\_ Date: \_\_\_\_\_

Medical Team Leader: \_\_\_\_\_

Date: \_\_\_\_\_

## Clinical Review

### 1. Background

Mecasermin rinfabate (trade name: iPLEX) is recombinant human insulin-like growth factor-I (rhIGF-I) complexed non-covalently with recombinant human insulin-like growth factor binding protein-3 (rhIGFBP-3). Inmed Inc. submitted a New Drug Application for iPLEX on January 3, 2005 (NDA 21-884). The indication sought is treatment of \_\_\_\_\_ children with growth hormone insensitivity syndrome (also called primary IGF-I deficiency). On September 26, 2005 the division issued an "Approvable Letter" listing multiple CMC deficiencies (there were no clinical approvability issues). On October 12, 2005 Inmed Inc. submitted a Complete Response to the September 26, 2005 Approvable Letter that includes the following: a response to CMC deficiencies, revised labels (PI, PPI, vial and carton labels), a clinical safety update, a non-clinical safety update, a post-approval immunogenicity monitoring plan, and a copy of the most recent submission made to the Office of Orphan Products Development that relates to orphan exclusivity issues. This review covers the clinical safety update and the iPLEX labeling (PI and PPI).

### 2. Clinical data sources

In this submission the applicant provides updated clinical safety data derived from (1) the on-going mecaseimermin rinfabate study INSM-110-303 conducted in primary IGFD patients and (2) from several non-primary IGFD investigations (mostly investigator sponsored studies).<sup>1</sup> This review is focusing on study INSM-110-303. The new clinical data collected in this trial are limited. Specifically, the application contains approximately two months of new safety information for the 29 patients described in the original NDA ("Cohort # 1" and "Cohort # 2") and safety data for a new cohort of patients ("Cohort # 3") treated with the to-be-marketed drug product (the "Boulder" drug product). The seven subjects from Cohort # 3 contribute approximately 1-month of safety data to this submission.<sup>2</sup> Adverse event data for 4 of these 7 patients have already been submitted to the agency on August 15, 2005, and were reviewed and summarized in the NDA review (see review in DFS).

<sup>1</sup> They include studies conducted in patients with type 1 diabetes, \_\_\_\_\_ Most of these studies were conducted in adult patients in conditions that are quite distinct from primary IGFD. The \_\_\_\_\_ population is the only pediatric one; it includes 33 patients enrolled in a single dose study of 1 mg/kg; no SAEs were reported to date. Of note, in the \_\_\_\_\_ study one adult patient with HIV and multiple allergies had an allergic reaction to iPLEX (SAE) that resolved without sequelae. A small number of patients with GHIS were followed in a compassionate use study. No SAEs were recorded in this study.

<sup>2</sup> No efficacy data are provided because assessment of efficacy requires a minimum of 3-6 months of treatment.

### 3. Exposure

With the addition of the safety update clinical data, the extent of exposure to iPLEX in the pivotal study INSM-110-303 is as follows:

- Cohort #1: 19 subjects treated for an average of 13.9 months
- Cohort #2: 10 subjects treated for an average of 7.9 months each
- Cohort #3: 7 subjects treated for approximately 1 month.

The current total exposure to iPLEX in GHIS subjects is 349 subject-months, or 29.1 subject-years.

### 4. Demographics

The demographics for the Cohort # 3 subjects who have completed postbaseline safety assessments (n=7) are presented in Applicant's Table 6, along with demographics for the other cohorts. Cohort # 3 includes 3 males and 4 females; 6 subjects were Caucasians and one subject was Asian. All 7 subjects are pre-pubertal with a mean age of 9.9 years (range 6.2 to 13.0 years). Five subjects have GH receptor deficiency, one subject has GH gene deletion, and one subject has a GHIS diagnosis of as yet unknown etiology. Mean baseline height SDS is -6.8.

#### Summary of Demographic and Other Characteristics in Primary IGFD Trial INSM-110-303.

Variable	INSM-110-303			
	Cohort #1 (n=19)	Cohort #2 (n=10)	Cohort #3 (n=7)	All Cohorts (n=36)
<b>GHIS Diagnosis (n, %)</b>				
GH Receptor Deficiency	17 (89%)	10 (100%)	5 (71%)	32 (89%)
GH Gene Deletion	2 (11%)	0 (0%)	1 (14%)	3 (8%)
Not Reported	0 (0%)	0 (0%)	1 (14%)	1 (3%)
<b>Sex (n, %)</b>				
Male	13 (68%)	4 (40%)	3 (43%)	20 (56%)
Female	6 (32%)	6 (60%)	4 (57%)	16 (44%)
<b>Race (n, %)</b>				
Caucasian	13 (68%)	9 (90%)	6 (86%)	28 (78%)
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	6 (32%)	0 (0%)	1 (14%)	7 (19%)
Other	0 (0%)	1 (10%)	0 (0%)	1 (3%)
<b>Pubertal Stage (n, %)</b>				
1 (pre-pubertal)	19 (100%)	10 (100%)	7 (100%)	36 (100%)
2-5 (pubertal)	0	0	0	0
<b>Age (yr)</b>				
n	19	10	7	36
Mean ± SD	8.4 ± 2.9	8.6 ± 3.9	9.9 ± 2.4	8.7 ± 3.1

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### 5. Common Adverse Events with iPLEX – an update

The adverse event profile of iPLEX in Cohort #1 (N=19) has not changed significantly from that reported in the original NDA submission. The most common adverse events are injection site conditions [including erythema (13 subjects, 68%), lipohypertrophy (12 subjects, 63%), and hair growth (10 subjects, 53%)], headache (37%), hypoglycemia (37%), hindered nasal breathing and/or tonsillar hypertrophy (16 %).

The most common adverse events reported in Cohort #2 are injection site hair growth (60%), injection site hypertrophy (50%), upper respiratory tract infection (50%), injection site erythema (40%), hyperglycemia (40%), and hypoglycemia (30%).

The most common adverse events reported in Cohort #3 to date are injection site conditions [injection site erythema (71%), injection site pruritis (29%), and injection site pain (14% or 1 subject)] and hypoglycemia (14%). The adverse events reported were all rated mild in intensity.

For all cohorts combined, the most common treatment-related adverse events occurring in 2 or more (> 5%) subjects were iron deficiency anemia, lymphadenopathy, thyromegaly, injection site conditions, increased transaminases, hyperglycemia, hypoglycemia, arthralgia, bone pain, muscular atrophy, pain in an extremity, headache, papilledema, hematuria, ovarian cysts, and tonsillar hypertrophy. Hypoglycemia was reported in 11/36 (31%) patients; headaches<sup>3</sup> were reported in 8/36 (22%) patients; tonsillar and/or adenoid hypertrophy were reported in 7/36 (19%) patients (2 patients underwent tonsillectomy and/or adenoidectomy).

## 6. Comparison of the safety profiles of iPLEX and rhIGF-I in Insmed's own database

In the original NDA submission the applicant provided a comparative analysis of adverse event incidence in the registration clinical trials of iPLEX and rhIGF-1, respectively, in patients with primary IGF-1 deficiency.<sup>4</sup> Specifically, this analysis compared six months of safety data from the Pharmacia clinical studies 90-111/92-5302-001 of rhIGF-1 with six months of safety data from Insmed's pivotal study INSM-110-303.<sup>5</sup> Only 19 subjects treated with iPLEX were included in this analysis. With the Complete Response this analysis has been extended to 29 subjects treated with iPLEX.

Taking into consideration the small size of the two datasets and the limited exposure (6 months), the two adverse event profiles appear to be generally comparable. For the first six months of iPLEX treatment 29 (100%) subjects reported a total of 177 adverse events (6.1 events per subject). On rhIGF-1, 26 (79%) of 33 subjects reported a total of 148 adverse events (4.5 events per subject) for the same duration of treatment. The most frequent adverse events reported in the iPLEX trial INSM-110-303 were injection site erythema (59%), injection site reaction (hair growth, 52%), injection site hypertrophy (41%), hypoglycemia (34%), upper respiratory tract infection (34%), headache (28%), and injection site pigmentation changes (24%). The most frequent adverse events following rhIGF-1 treatment in the Pharmacia study were headache (33%), injection site pain (30%), hypoglycemia (21%), and pyrexia (18%). Interestingly, in this analysis, hypoglycemia incidence was lower with rhIGF-1. The applicant points out that severe adverse events were recorded more frequently with rhIGF-1 relative to iPLEX<sup>6</sup> and concludes that, "although the overall incidence of adverse events with rhIGF-1 and rhIGF-1/rhIGFBP-3 in GHIS was similar for most event types, the severity of significant adverse events such as hypoglycemia

<sup>3</sup> An adverse event of increased intracranial pressure and papilledema (possible intracranial hypertension) was also reported, which resolved with the revision of a blocked existing ventriculo-peritoneal shunt.

<sup>4</sup> Insmed acquired the property rights to Pharmacia's rhIGF-1 data:

It has been, reportedly, approved but not marketed in Europe.

<sup>5</sup> The applicant recoded under blinded conditions the adverse events of the Pharmacia studies in order to "ensure an equitable comparison of adverse events reported during Clinical Studies INSM-110-303 and 90-111/92-5302-001."

<sup>6</sup> 13 (39%) with rhIGF-1 and 2 (7%) with iPLEX.

was greater with IGF-I.” To this end, an analysis that compares serious adverse events (SAEs) in the two above-mentioned datasets, suggests a higher incidence of SAEs in the rhIGF-I dataset.<sup>7</sup> The adverse events that occurred more frequently with rhIGF-1 were hypoglycemia, headache, convulsions, papilledema, hypokalemia, agitation, dizziness, gastroenteritis, hypotonia, paralysis, renal pain, sepsis, and surgical intervention. Such SAEs included a mixture of adverse events that can be linked mechanistically to IGF-1 (hypoglycemia,<sup>8</sup> headache,<sup>9</sup> convulsions,<sup>10</sup> papilledema<sup>11</sup>) and others that do not. Adverse events that occurred more frequently in association with iPLEX were cardiorespiratory failure, gastrostomy tube insertion, hepatomegaly, and obstructive bronchitis. It is important to note that applicant’s analysis has major limitations related to (1) the short duration of exposure (first 6 months of treatment), (2) the small size of the datasets, and (3) the post-hoc and historical nature of the comparison (the two treatments were not compared in the same clinical trial).<sup>12</sup>

## 7. Immunogenicity of iPLEX

The immunogenicity information submitted in the original NDA at the Month 6 timepoint for patients in Cohort # 2 is updated in this submission with a Month 9 timepoint. Applicant’s Table 13 provides this update, which represents the basis for the immunogenicity information in the currently proposed label.

**Table 13. Antibody Incidence and Titer in Cohort #2.**

	Month 1	Month 3	Month 6	Month 9	(+) at any Timepoint
<b>Anti-IGF-1 Ab</b>					
(+) Subjects (%)	0/10 (0%)	0/10 (0%)	1/9 (11%)	2/8 (25%)	2/10 (20%)
Titer, Mean	0	0	18	85	
Titer, Median	0	0	0	0	
<b>Anti-IGFBP-3 Ab</b>					
(+) Subjects (%)	2/10 (20%)	3/10 (30%)	1/9 (11%)	0/8 (0%)	5/10 (50%)
Titer, Mean	136	12	4.4	0	
Titer, Median	0	0	0	0	
<b>Anti-IGF-1/IGFBP-3 Ab</b>					
(+) Subjects (%)	3/10 (30%)	6/10 (60%)	7/9 (78%)	7/8 (88%)	9/10 (90%)
Titer, Mean	44	136	302	190	
Titer, Median	0	80	80	80	

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In response to a request formulated in the September 26, 2005 Approvable Letter, the applicant agrees to provide “longer-term” clinical data related to the immunogenicity of iPLEX following approval. Such information will be reported on an annual basis until the completion of the 2-year INSM-110-303 study.

<sup>7</sup> During the first six months of treatment with iPLEX, four (14%) of 29 subjects experienced a total of 8 (0.28 per subject) serious adverse events and one of them discontinued treatment because of a serious adverse event. Eleven (33%) of 33 subjects experienced a total of 21 (0.64 per subject) serious adverse events during the first six months of treatment with rhIGF-1.

<sup>8</sup> 4 (12%) with rhIGF-1 and 2 (7%) with iPLEX.

<sup>9</sup> 2 (6%) with rhIGF-1 and none with iPLEX.

<sup>10</sup> 1 (3 %) with rhIGF-1 and none with iPLEX.

<sup>11</sup> 1 (3 %) with rhIGF-1 and none with iPLEX.

<sup>12</sup> In support of the idea that severe adverse events occur more frequently in association with rhIGF-I relative to iPLEX, the applicant also submits a meta-analysis that compares the adverse event profile of rhIGF-1 against rhIGF-1/rhIGFBP-3 in patients with diabetes. This meta-analysis, performed by Clemmons et al. from published literature includes data derived from 3 studies with rhIGF-1 and 2 studies with rhIGF-1/rhIGFBP-3. It indicates a higher incidence for several AEs during rhIGF-1 treatment relative to rhIGF-1/rhIGFBP-3 treatment. Statistically significant differences were demonstrated for peripheral edema, facial edema, jaw pain, and arthralgias. This analysis has not been reviewed independently by the agency.

The immunogenicity data will be collected and analyzed using the same methods described in the original NDA and subsequent submissions such as the 120-day Safety Update and the September 13, 2005 update (all previously reviewed).

## 8. Summary and Conclusions

The new clinical information submitted in this safety update can be summarized as follows:

- There were no deaths reported.
- There were no unexpected SAEs.<sup>13</sup>
- There were no new adverse events that resulted in patient discontinuation/withdrawal from treatment.
- There were no significant changes in the incidence of common adverse events.
- There were no new findings in laboratory testing, physical exams and vital signs.
- The clinical information derived from the non-primary IGFD populations studied did not raise any previously unidentified safety concerns/signals.

In final analysis there are no new clinical safety signals or new issues generated by the results of this clinical safety update. There is no disagreement between this reviewer's conclusions and those of the applicant's with respect to the results presented for the registration clinical trial INSM-110-303. There are no changes in this reviewer's recommendation for iPLEX approval from a clinical perspective.

## 9. Labeling

Updated labeling (PI and PPI) are attached.

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<sup>13</sup> One SAEs was reported in primary IGFD patients (adenoidectomy for adenotonsillar hypertrophy); this adverse event has been described previously (and labeled) and is consistent with the known mechanism of action of iPLEX.

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     § 552(b)(4) Trade Secret / Confidential

     § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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## CLINICAL REVIEW

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Submission Number 21-884  
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Letter Date 12/31/2004  
Stamp Date 01/03/2005  
PDUFA Goal Date 10/3/2005

Reviewer Name Dragos Roman  
Review Completion Date 09/23/2005

Established Name Mecasermin rinfabate  
(Proposed) Trade Name iPLEX  
Therapeutic Class Recombinant Human Insulin-like Growth  
Factor-I  
Applicant Insmed Incorporated  
Priority Designation P

Formulation injectable  
Dosing Regimen 1-2 mg/kg daily subcutaneously  
Indication Severe short stature  
Intended Population Children with primary IGF-I deficiency

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Clinical Review  
{Dragos Roman}  
{21-884/N000}  
{Mecasermin rinfabate (iPLEX)}

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

From a clinical perspective, mecasermin rinfabate 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).<sup>1</sup>

Accepting the limitations of a baseline-controlled clinical trial and the fact that a placebo-controlled 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 rinfabate has an acceptable benefit-to-risk profile for the proposed indication if used according to the label. Mecasermin rinfabate treatment was effective in increasing linear growth short-term in patients with severe primary IGFD at to-be-marketed doses of 1-2 mg/kg daily. The adverse event profile of mecasermin rinfabate, 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 for rhIGF-I; it is also consistent with IGF-I's known mechanisms of action. In general there are no major differences between this reviewer's and applicant's efficacy and safety conclusions.

### **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 rinfabate as an anabolic agent.

#### **1.2.2 Required Phase 4 Commitments**

None.

#### **1.2.3 Other Phase 4 Requests**

There are unanswered questions concerning the long-term treatment with mecasermin rinfabate, in particular as it relates to the immunogenicity of the product and the theoretical risk of developing neutralizing antibodies (in contrast to endogenous IGFBP-3, rhIGFBP-3 is not

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<sup>1</sup> In order to harmonize the indication for this product with that of the recently approved recombinant human IGF-I (brand name: Increlex), this reviewer recommends to use the term "primary IGF-I deficiency" (primary IGFD) instead of "hereditary growth hormone insensitivity syndrome" (GHIS) proposed by the applicant. These two terms will be used interchangeably in the review.

glycosylated). Although the data presented to date do not indicate any evidence of neutralizing antibodies, this theoretical risk should be investigated postapproval. The applicant should continue to measure antibodies against rhIGF-I/rhIGFBP-3 and its components and collect long-term efficacy data for height velocity and height SDS<sup>2</sup> with the aim of obtaining final height information.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Mecasermin rinfabate (proposed trade name: iPLEX) is recombinant human insulin-like growth factor-I (rhIGF-I) complexed non-covalently with recombinant human insulin-like growth factor binding protein-3 (IGFBP-3).<sup>3</sup> These two components of the rhIGF-I/rhIGFBP-3 complex are produced separately by recombinant DNA technology in E.coli. RhIGF-I is a single chain polypeptide containing 70 amino acid residues and is identical to the human native IGF-I, which is the main mediator of growth hormone's actions on linear growth. RhIGFBP-3 (a single chain polypeptide containing 264 amino acids, identical in primary structure to native human IGFBP-3 but not glycosylated) is the major circulating IGF-I binding-protein.<sup>4</sup>

Mecasermin rinfabate has been developed under the premise that administering IGF-I in a compound that contains its major binding protein (IGFBP-3) is more physiological and, in addition, will reduce the frequency of injections needed (rhIGF-I is given twice a day while mecasermin rinfabate is given daily). It has also been proposed that rhIGF-I/rhIGFBP-3 may reduce the risk of hypoglycemia observed with rhIGF-I alone.<sup>5</sup>

The proposed indication for mecasermin rinfabate is ' — treatment of children — with growth failure due to severe growth hormone insensitivity syndrome (hereditary or acquired) resulting in IGF-I deficiency and presenting with height standard deviation score — less than or equal to - 3 and IGF-I SDS less than or equal to — Growth hormone (GH) insensitivity syndrome, also called primary IGF-I deficiency, is a state of GH resistance and is due to a variety of molecular defects<sup>6</sup> that all converge into a similar phenotype: severe short stature.

Mecasermin rinfabate is a new drug combination.<sup>7</sup> It is given as a single daily subcutaneous injection — meal at an initial dose of 0.5-1 mg/kg to be titrated up to a

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<sup>2</sup> Height SDS = height standard deviation score.

<sup>3</sup> In this review mecasermin rinfabate and rhIGF-I/rhIGFBP-3 will be used interchangeably.

<sup>4</sup> Following the binding of IGF-I to IGFBP-3, a ternary complex is formed by binding to another serum protein: acid labile subunit (ALS). The ternary complex is responsible for the gradual release of circulating IGF-I from a bound state to free IGF-I, which can cross outside the vascular space and reach the target tissues.

<sup>5</sup> IGF-I (and rhIGF-I) is capable of binding the insulin receptor albeit with lower affinity than insulin itself (it has < 10% of the glucose-lowering effect of insulin) and may cause hypoglycemia.

<sup>6</sup> Such defects have been described at the level of the GH receptor (Laron syndrome), in postreceptor signaling pathways and in the IGF-I gene.

maximum dose of 2 mg/kg, depending on patients' tolerability (i.e. presence or absence of hypoglycemia) and serum IGF-I levels. The treatment is to be initiated in early childhood and continued up to the point of epiphysial closure.

Mecasermin rinfabate has been studied in one clinical trial (INSM-110-303) that enrolled 29 patients in two non-randomized cohorts: Cohort # 1, which includes 19 patients treated for 12 months with a development drug substance (manufactured in Santa Clara, California) at 1 mg/kg and Cohort # 2, which includes 10 patients treated for 6 months with what was supposed to be the commercial drug substance (manufactured at Avecia, UK) at a final daily dose of 2 mg/kg. The mean duration of treatment with mecaseermin rinfabate in Cohort # 1 is  $11.3 \pm 2.6$  months and the total exposure is 215 subject-months; the mean duration of treatment for Cohort # 2 is  $5.4 \pm 0.8$  months (total exposure 54 months). As plans to use the Avecia manufacturing site were changed, the applicant proposes to manufacture the to-be-marketed drug substance at a new facility in Boulder, Colorado, using the same manufacturing process as the one used for the "Avecia" product. Bioequivalence between the "Avecia" and the "Boulder" drug substance was established in healthy volunteers.

A major limitation of clinical trial INSM-110-303 is the absence of a control group, which makes an accurate interpretation of the incidence of adverse events difficult. However, it would be unethical to treat GHIS patients with placebo or to enroll a no-treatment control group when rhIGF-I has been clearly shown to have statural growth benefits in multiple clinical studies. It is important to recognize that Laron syndrome is a relatively well characterized condition and growth charts specific for patients with Laron Syndrome are currently available. Patients with GHIS, if appropriately diagnosed, are not anticipated to exhibit spontaneous correction of their growth deficits (i.e. growth acceleration on mecaseermin rinfabate in this patient population is drug-related).

### 1.3.2 Efficacy

Mecasermin rinfabate was effective in increasing short-term linear growth in patients with severe growth hormone insensitivity syndrome due to either Laron syndrome or GH gene deletion and neutralizing antibodies to GH.

In a cohort of 16 evaluable patients treated at a daily rhIGF-I/rhIGFBP-3 dose of 1 mg/kg with the development drug product,<sup>8</sup> the mean height velocity almost doubled during 12 months of treatment (it increased from  $3.4 \pm 1.9$  cm/yr. at baseline to  $6.4 \pm 1.6$  cm/yr. at Month 12 ( $p=0.0018$  compared to pre-treatment HV; primary efficacy analysis). The mean change in height velocity from pre-treatment to Month 12 was  $3.0 \pm 1.3$  cm/yr (range: — cm/yr;

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<sup>7</sup> RhIGF-I has been recently approved (August 30, 2005) under the brand name INCRELEX for the same indication.

<sup>8</sup> Average dose for the entire cohort: 0.96 mg/kg. Drug substance manufactured at the Santa Clara, California facility.

95% C.I. = 2.3-3.7 cm/yr).<sup>9</sup> At Month 6 all patients had a HV increase > 2 cm/yr. and 6/16 (38%) had an increase > 4 cm/yr. At Month 12, 12/16 (75%) had a HV increase > 2 cm/yr. and 6/16 (38%) had an increase > 4 cm/yr.

In a second cohort of 9 evaluable patients titrated to a dose of 2 mg/kg for 6 months with what was intended to be the commercial product,<sup>10</sup> the mean height velocity changed from 2.2 ± 1.5 cm/yr (pre-treatment) to 8.8 ± 2.0 cm/yr at Month 6 (p < 0.0001 relative to baseline). The mean change in height velocity was 6.6 ± 2.6 cm/yr from pre-treatment to Month 6 (95% CI: 4.6 to 8.6 cm/yr). For this “commercial product” all subjects increased height velocity by at least 2 cm/yr, with 7/9 (78%) subjects having an increase of at least 4 cm/yr.<sup>11</sup>

When the efficacy data at Month 6 were compared between the “low dose” (Cohort # 1) and the “high dose” (Cohort # 2) groups, the latter appeared to be more effective (HV change from baseline of 6.6 ± 2.6 cm/yr vs. 4.0 ± 1.8 cm/yr). However, it is important to recognize that patients were not randomized but were rather assigned to the two different dose regimens, thus limiting the ability to draw firm conclusions about dose-response to rhIGF-I/rhIGFBP-3.<sup>12</sup>

The change in mean height standard deviation score or height SDS (a secondary efficacy analysis) for Cohort 1 at Month 12 was 0.5 ± 0.4 (p = 0.0017).<sup>13</sup> The changes in mean height SDS at Month 6 were 0.3 ± 0.2 for Cohort # 1 (p < 0.0001), and 0.42 ± 0.25 for Cohort # 2 (p = 0.0009).<sup>14</sup>

The changes in height velocity and height SDS did not appear to be associated with an excessive acceleration in bone age.<sup>15</sup> The predicted adult height increased with treatment but one needs to recognize the exploratory quality of this analysis since methods of height prediction have not been validated in patients with GHIS.

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<sup>9</sup> Two subjects with GH gene deletion and antibodies to GH had height velocities at Month 12 of — cm/yr and HV changes from baseline of — cm/yr, respectively. These results were comparable with those observed for the whole group of subjects.

<sup>10</sup> Mean daily dose of 1.4 mg/kg. Drug substance manufactured at the Avecia (UK) facility.

<sup>11</sup> It is important to recognize that the 6-month annualized height velocity overstates the annual height velocity because catch up growth during the first year of treatment is more rapid for Months 0-6 relative to Month 6-12.

<sup>12</sup> For the 25 patients (of the 29 enrolled) with data at the Month 6 timepoint (combined Cohorts # 1 and # 2), rhIGF-I/rhIGFBP-3 (at an average daily dose of 1.1 mg/kg) more than doubled the mean height velocity from 3.0 ± 1.8 cm/yr to 7.9 ± 2.1 cm/yr. The mean change in HV relative to baseline was 5.0 ± 2.4 cm/yr and was statistically significant (p < 0.0001). All subjects had a HV increase of at least 2 cm/yr.

<sup>13</sup> After 12 months of therapy, the increase in height SDS was at least 0.3 in 14/16 (88%) subjects and at least 0.5 in 10/16 (63%) subjects.

<sup>14</sup> For the 25 patients with data at the Month 6 timepoint (combined Cohorts # 1 and # 2), the mean height SDS at 6 months was 0.4 ± 0.2 (p < 0.0001).

<sup>15</sup> For Cohort # 1 the mean bone age change from baseline was 1.5 ± 0.8 yr and 1.4 ± 0.6 yr (two different methodologies were employed) over one year of treatment. For the “commercial product” (Cohort # 2) the bone age change was 1.1 ± 0.4 yr and 0.7 ± 0.4 yr, relative to 6 months of treatment. Because patients with GHIS have bone age delay, bone age maturation on treatment is expected to display a “catch up” phenomenon and to exceed to some extent chronological age.

There is no information available regarding the efficacy of mecaseimerin rinfabate beyond one year of treatment.

When the efficacy results obtained with mecaseimerin rinfabate in clinical trial INSM-111-303 are compared descriptively with published efficacy results obtained with rhIGF-I, they are comparable (this is particularly evident for the “high” dose regimen of 2 mg/kg daily).

Finally and importantly, during this review cycle Insmmed informed the division that the drug substance to be included in the to-be-marketed drug product will no longer be manufactured at the Avecia facility as initially planned. Instead, a new drug substance will be manufactured at Insmmed’s new facility in Boulder, Colorado using the same manufacturing process. In order to establish pharmacokinetic equivalency between the “Avecia” and “Boulder” drug products the applicant conducted a bioequivalence study in healthy volunteers. The results of this study have been reviewed by the clinical pharmacology reviewer and found to be acceptable (i.e. the two products are bioequivalent). According to the chemistry reviewer there is no substantive change in the manufacturing process between the Avecia and Boulder sites. No efficacy data are available to date with the “Boulder” drug product;<sup>16</sup> limited safety data (< 1 month exposure) obtained with this product is presented in the next section. However, given the fact that the manufacturing process has not changed and that the two drug substances are bioequivalent, the “Boulder” product is expected to have the same efficacy and safety profile as the “Avecia” product.

### 1.3.3 Safety

In presenting the safety findings of clinical trial INSM-110-303 it is important to acknowledge the following: (1) there is no comparator group against which the incidence of adverse events can be evaluated<sup>17</sup>; (2) the clinical dataset is small in absolute numbers (29 patients) but taking into consideration the prevalence of Laron syndrome (approximately 350 patients worldwide) this is a considerable proportion of patients with this disease worldwide<sup>18</sup>; (3) the exposure to the study drug is relatively short (6-12 months) but the long-term safety profile for rhIGF-I itself is well described in published reports; (4) the safety data in this trial were collected prospectively. The major findings of the safety review are summarized next.

There was one death reported in a patient with Laron syndrome and endocardial fibroelastosis which was due to a respiratory syncytial viral (RSV) infection (RSV infections are known to take a lethal course in children with concomitant heart disease). Importantly, the autopsy report indicates that the patient’s endocardial fibroelastosis preceded the enrollment in the clinical

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<sup>16</sup> Assessment of linear growth requires a minimum of 3-6 months of treatment.

<sup>17</sup> As previously mentioned it would be unethical to treat GHIS patients with placebo or to enroll a no-treatment control group when rhIGF-I has been clearly shown to have statural growth benefits in multiple clinical studies.

<sup>18</sup> In addition, the natural course of the disease has been extensively researched by several investigators and described in detail in multiple publications and standard textbooks.

trial.<sup>19</sup> This patient also had three SAEs of obstructive bronchitis, one of hepatomegaly and one of cardiorespiratory arrest.<sup>20</sup>

SAEs reported in other patients in the clinical trials were: (1) hypoglycemia (associated with brief hospitalization and subsequent dose reduction), (2) nighttime hypoglycemia (associated with loss of consciousness), (3) adenoid hypertrophy (requiring surgical removal of the adenoids), (4) papilledema/increased intracranial hypertension, and (5) gastrostomy tube placement. Based on the known mechanism of action of IGF-I, hypoglycemia, adenoid hypertrophy and increased intracranial hypertension are the SAEs most likely to have been caused by the study drug.<sup>21</sup>

Only one patient discontinued participation in the trial due to an adverse event (hepatomegaly, previously described).

There were no reports of cancer in the clinical trial.

The most common treatment-emergent adverse events (TEAEs) across both cohorts studied were those related to the injection site. They were captured under a variety of terms such as erythema (58.6 %), “reaction” (55.2 %), hypertrophy (51.7 %), pigmentation changes (27.6%), induration (17.2 %), pain (10.3 %), and pruritus (6.6%). Other TEAEs that occurred in  $\geq 3$  ( $\geq 10$  %) patients were upper respiratory tract infection (34.5 %), hypoglycemia (34.5 %),<sup>22</sup> headache (24.1 %), hyperglycemia and tonsillar hypertrophy (13.8 % each).

Several TEAEs were always considered treatment-related by the investigators. Among the frequent TEAEs of Cohort # 1 injection site conditions, hypoglycemia, bone pain, muscular atrophy, pain in extremity, and tonsillar hypertrophy were always considered treatment-related (headache was another adverse event which, in a large proportion of patients, was deemed treatment-related). Frequent TEAEs considered treatment-related by the investigators in all cases in Cohort # 2 were those related to the injection site, hypoglycemia, increased transaminases, hematuria, and tonsillar hypertrophy. Infrequent TEAEs (occurring in only one patient) that were considered treatment-related were lymphadenopathy, ear pain, tooth disorder, crying, hunger, injection site urticaria, “therapeutic response decreased,” hepatomegaly, hepatic steatosis (ultrasound finding), arthralgia, ovarian cyst, milia, and pruritus (all in Cohort # 1) and

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<sup>19</sup> This patient withdrew from the clinical trial after approximately 5 months of treatment. The translated pathology report states that the heart had “massive endocardial fibroelastosis of each cavities of the heart” [...] and that “the patient has to be suffered from the endocarditis long-termed at least 9 months” [i.e. prior to the enrollment in the clinical trial]. The report concludes that the patient’s death was attributed to “a firstly respiratory failure and secondary heart failure consolidated by an long-term proceeded fibrous endocarditis.”

<sup>20</sup> Of these, only the hepatomegaly SAE was deemed possibly treatment-related by the investigator, while all others were judged as “not related.” The last episode of obstructive bronchitis was concomitant with the fatal illness. The two previous episodes of obstructive bronchitis and that of hepatomegaly preceded closely the fatal illness.

<sup>21</sup> Two additional SAEs were reported with the to-be-marketed “Boulder” drug product: hospitalization for weight loss and management of gastrostomy tube feedings (“not related”) and tonsillar/adenoid hypertrophy leading to adeno-tonsillectomy (“possibly related”).

<sup>22</sup> Most TEAEs of hypoglycemia were mild in intensity. One was reported as moderate (required glucose gel ingestion). For severe hypoglycemic manifestations see SAEs associated with hypoglycemia above.

iron deficiency anemia, splenomegaly, hypothyroidism, ovarian cyst, and pulmonary hypertension (all in Cohort # 2).<sup>23</sup>

Several special assessments were conducted during the clinical trial to evaluate the possibility of excessive organ growth and associated complications. They included abdominal ultrasounds (measuring in particular kidney and spleen size) and audiograms. The pattern observed on abdominal ultrasounds was that of initial rapid catch up growth followed by a subsequent slowdown in organ growth rates, similar to the pattern seen with linear growth. Audiogram results suggest that hearing loss may be associated with mecaseimerin rinfabate treatment in some patients who develop excessive adenoid tissue growth and chronic ear effusions.

Fundoscopy exams did not show any evidence of retinopathy.

Echocardiographic evaluations identified two patients with valvular disease but none had clinical correlates.<sup>24</sup> A causal link between occasional echocardiographic (valvular) findings observed during the clinical trial and mecaseimerin rinfabate treatment cannot be made at this point in absence of a control group and mechanistic plausibility.

There were no changes in mean values for standard laboratory tests such as hematology (CBC) and chemistry (electrolytes, BUN, creatinine, LFTs). Nor were any outlier measurements for any of these analytes. A large proportion of patients had elevated AST and LDH measurements at baseline and at subsequent visits. Two patients had ALT elevations and required interruption of therapy for 10 days and 1.5 months, respectively. Overall there were three individual ALT values in three patients which were > 2X ULN (but < 3X ULN); none was associated with bilirubin elevations.

Mean vital sign measurements and ECGs were normal.

A potential risk of antigenicity for mecaseimerin rinfabate was anticipated due to the fact that the rhIGFBP-3 moiety of mecaseimerin rinfabate is not glycosylated (this is in contrast to the endogenous IGFBP-3 which has several glycosylation sites).<sup>25</sup> The development drug product

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<sup>23</sup> During the review cycle the applicant submitted limited safety information obtained with the to-be-marketed drug product manufactured at the Boulder (Colorado) site. This report includes safety data on 4 subjects from Cohort # 2 who switched from the "Avecia" drug product to the "Boulder" drug product. The duration of exposure is very short (3 weeks). All patients received 2 mg/kg of rhIGF-I/rhIGFBP-3 daily. Five adverse events were reported in 2 of the 4 subjects. They were dry skin ("not related"), microscopic hematuria, iron deficiency anemia, injection site lipohypertrophy, and worsening of congenital hip dislocation (the latter four were considered "possibly related"). A subsequent submission included one month of safety data obtained from four treatment-naïve patients treated for one month with the "Boulder" drug product; six TEAEs were reported in these four patients (all related to the injection site and rated as mild in intensity).

<sup>24</sup> One patient in Cohort # 1 (mild tricuspid regurgitation) and one patient in Cohort # 2 (tricuspid insufficiency). Another patient was identified with moderate mitral valve stenosis but this patient had endocardial fibroelastosis that preceded the trial enrollment.

<sup>25</sup> In Cynomolgus monkeys 90 day administration of two doses (1 mg/kg and 10 mg/kg) of rhIGF-I/rhIGFBP-3 in the same buffer composition as the proposed human product was associated with the development of anti-rhIGF-I/rhIGFBP-3 antibodies in all animals and accumulation of serum IGF-I. When tested, the antibodies were not

(“Santa Clara”) was remarkably immunogenic: 12/15 (80 %) patients developed anti-IGF-I antibodies, 10/15 (67 %) had anti-IGFBP-3 antibodies and 14/15 (93 %) had anti-IGF-I/IGFBP-3 antibodies at 12 months. The “commercial” or “Avecia” drug product was less immunogenic: at 6 months only 1/9 (11%) of patients had anti-IGF-I or anti-IGFBP-3 antibodies; however, a significant proportion of patients (7/9 or 78 %) still had anti-IGF-I/IGFBP-3 antibodies. The mean antibody titers were markedly lower in the “Avecia” product relative to the “Santa Clara” product. This phenomenon is likely due to the — in the “Avecia” drug product. Testing for neutralizing antibodies using an in vitro IGF-I bioassay in a subgroup of patients at Months 6-9 (Cohort # 1) was negative (i.e. no evidence of neutralizing antibodies).<sup>26</sup> The applicant did not find any correlation between antibody titers and reduction of the effect on HV during treatment.

### **Safety conclusions:**

Despite the absence of a control group that would perhaps permit differentiation of the adverse events associated with mecasermin rinfabate treatment from background 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 and should be included in the label:

- As expected from the known insulinomimetic mechanism of action of IGF-I and from the published data obtained with rhIGF-I, mecasermin rinfabate can cause hypoglycemia, which occasionally can be severe.
- Hypertrophy/rapid growth of the lymphoid tissues (tonsillar, adenoid, splenic) occurs during mecasermin rinfabate treatment. Secondary complications (chronic middle ear effusions, hearing loss, sleep apnea, and need for tonsillectomy/adenoidectomy) can occur and should be monitored for. They are treatable, should they occur.
- Injection site reactions are frequent and should be explicitly described in the label along with strategies to minimize their occurrence (injection site rotation).
- Although no neutralizing antibodies have been identified to date, a large proportion of patients developed antibodies to the rhIGF-I/rhIGFBP-3 complex. Combined with the fact that the rhIGFBP-3 component of mecasermin rinfabate is not glycosylated (in contrast with the native human IGFBP-3) there is at least a theoretical risk that patients may develop in time neutralizing antibodies. This theoretical risk should be labeled so that practicing physicians investigate promptly any loss of efficacy on treatment.
- As IGF-I is the main mediator of GH actions and since adverse events similar to those described in association with GH treatment have been observed with mecasermin rinfabate even in a small dataset (e.g. arthralgia, hypothyroidism, and papilledema), it is likely that in a larger patient population and with additional patient exposures to mecasermin rinfabate additional GH-associated adverse events will be observed in the future. Therefore, it is prudent to mention this class of adverse events in the mecasermin rinfabate label.

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neutralizing in an in vitro IGF-I bioassay.

<sup>26</sup> Patients assayed were selected for testing on the basis of high antibody titers and/or lowest height velocity on treatment.

- Two adverse events of ovarian cysts were reported. Although, as for most adverse events causality cannot be demonstrated, ovarian cyst formation is one of the labeled AEs for the rhIGF-I product approved in Japan.
- Since a large proportion of patients had abnormal serum analyte measurements at baseline and at subsequent visits (e.g. AST, LDH) this should be labeled as such.
- Two patients had AST elevations that required temporary interruption of mecasecmin treatment (one patient continued the treatment without further incidents, the other was later discontinued from the trial for poor compliance).
- Facial soft tissue changes and mandibular growth have been described in the medical literature in association with long-term rhIGF-I treatment. Therefore, this potential risk should be mentioned in the label.
- Since IGF-I is very close functionally to GH the label should assert clearly that the two drugs are distinct and should not be used to replace each other for approved and labeled indications.
- The label should mention that efficacy and safety beyond one year have not been studied. Importantly, the applicant should further investigate postapproval the theoretical risk of developing neutralizing antibodies.

#### 1.3.4 Dosing Regimen and Administration

The applicant has investigated two dose regimens in the clinical trial INSM-110-303: 1mg/kg and 2 mg/kg (given as a single subcutaneous injection after the evening meal).<sup>27</sup> Both regimens appear safe and effective if appropriately labeled. The efficacy analysis of height velocity at Month 6 suggests that the higher dose may be associated with a better efficacy response. It is important to recognize, however, that patients were not randomized to the two drug regimens.<sup>28</sup> The small safety dataset available to date does not indicate a clear pattern of dose-dependent adverse events.

The titration regimen brought serum IGF-I levels within the normal range of -2 SD to + 2SD for most patients. Several outlier values were observed including a remarkable one (up to +20 SD).

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<sup>27</sup> The applicant chose the 1 mg/kg dose on the basis of a pharmacokinetic study in children with GHIS, which showed that “administration of 1.0 mg/kg of rhIGF-I/rhIGFBP-3 once daily was comparable to 80 µg/kg of rhIGF-I given twice daily in restoring mean peak IGF-I levels to within the normal range.” rhIGF-I has been given safely in children with GHIS in doses up to 120 µg/kg twice a day and the approved doses for Increlex (rhIGF-I) are 80-120 µg/kg BID.

<sup>28</sup> Patients were assigned somewhat arbitrarily to the low dose regimen of 1mg/kg dose in Cohort # 1 and, following reassuring efficacy and safety results with this dose, a second group of subjects (Cohort # 2) was titrated up to a 2 mg/kg daily dose based on serum IGF-I levels. The titration scheme recommended by the Steering Committee was as follows: if IGF-I SDS on treatment is ≤ 2: increase the daily dose by 1.0 mg/kg (maximum dose 2 mg/kg); if IGF-I SDS is between -2 and 0: increase daily dose by 0.5 mg/kg (maximum dose 2 mg/kg); if IGF-I SDS is between 0 and + 3: do not change the dose; if IGF-I SDS is > + 3 and/or intolerable side effects: decrease the daily dose by 0.5 mg/kg.

In Cohort # 1 two patients had their rhIGF-I/rhIGFBP-3 doses reduced due to excessive serum IGF-I levels; in Cohort # 2 all patients could be eventually titrated to the 2 mg/kg dose.

### 1.3.5 Drug-Drug Interactions

No drug interaction studies were conducted.

### 1.3.6 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, race or comorbid states (such as renal or hepatic failure) on mecaseimerin rinfabates's efficacy and safety.

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## 2.2 Currently Available Treatment for the Indication

Until recently there was no approved treatment for the primary IGFD indication in the US. Mecasermin (trade name: Increlex), which is a rhIGF-I product without the binding protein, has been approved for this indication on August 30, 2005.<sup>32</sup>

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

See comments in Section 2.2.<sup>33</sup>

## 2.4 Important Issues With Pharmacologically Related Products

There are two compounds that are mechanistically related to rhIGF-I/rhIGFBP-3. They are rhIGF-I or mecasermin (recently approved in the US under the brand name Increlex) and rhGH (several GH products have been approved in the US for decades). Since the action of rhIGF-I/rhIGFBP-3 is intimately connected with that of growth hormone (approximately 80% of the GH effect on growth is IGF-I mediated), adverse events such as pseudotumor cerebri, joint pain, myalgia, edema, unmasking of underlying hypothyroidism, slipped capital femoral epiphyses during rapid growth, gynecomastia, insulin resistance, all seen with GH, can be anticipated with rhIGF-I containing compounds, including rhIGF-I/rhIGFBP-3.<sup>34</sup>

## 2.5 Presubmission Regulatory Activity

An end-of-phase-2 meeting took place on June 4, 2003. At that meeting and in several subsequent written communications the division and the applicant discussed issues related to trial design, statistical analysis plan, and study duration. The applicant decided against a pre-NDA meeting because it did not fit with the planned date of the NDA submission. After NDA submission (January 3, 2005) the applicant met with the division to discuss issues related to the drug substance manufacturing site. The applicant also met with representatives of the Office of Orphan Product Development to discuss orphan exclusivity issues.

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<sup>32</sup> The labeled indication for Increlex is the long-term treatment of growth failure in children with severe primary IGF-I deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe Primary IGFD is defined by: height standard deviation score  $\leq -3.0$  and basal IGF-I standard deviation score  $\leq -3.0$  and normal or elevated growth hormone.

<sup>33</sup> Several rhIGF-I preparations have been approved for use in Europe and Japan. For instance, mecasermin (Somazon) was approved in Japan for two indications: (1) extreme insulin resistance and (2) Growth Hormone Insensitivity Syndrome (Growth Hormone Resistance due to Isolated Growth Hormone Deficiency Type IA and Laron Syndrome). RhIGF-I made by Pharmacia/Upjohn was approved in several European countries but was never commercialized.

<sup>34</sup> Indeed, such adverse events are labeled for Increlex (arthralgia, pain in extremity, intracranial hypertension).

## **2.6 Other Relevant Background Information**

Refer to Section 2.2

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

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

The CMC review is pending at this time.

The microbiology review (in DFS) recommends approval.

The clinical pharmacology reviewer recommends approval of the application (see clinical pharmacology review of Dr. Jim Wei). Specific labeling recommendations are included in the line-by-line review section.

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

The pharmtox. reviewer recommends approval of the application. Specific labeling recommendations are included in the line-by-line review section.

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

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

The main source of clinical efficacy and safety data for the current indication is clinical trial INSM-110-303, an open-label, baseline-controlled, multicenter clinical study of rhIGF-I/rhIGFBP-3 conducted in patients with growth hormone insensitivity syndrome (primarily Laron syndrome). The applicant also conducted several pharmacokinetic studies, some in healthy volunteers others in patients with GHIS (see Clinical Pharmacology Review and Section 5.1). In addition, the applicant has submitted data from 10 clinical studies of rhIGF-I/rhIGFBP-3, which include: three Phase I studies in healthy volunteers, a Phase I trial in children and adolescents with GHIS, a Phase 2 trial in elderly females with hip fracture, a Phase 2 trial in children and adults with severe burns, three Phase 2 trials in subjects with diabetes, and a compassionate use program. All these studies explored several rhIGF-I/rhIGFBP-3 doses as well as its efficacy and safety in a variety of patient populations. Due to the limited size of these trials and the short duration of treatment with rhIGF-I/rhIGFBP-3, and most importantly, due to the fact that the patient populations are clinically so different from GHIS syndrome, these small studies will not be summarized in this review.

## **4.2 Tables of Clinical Studies**

Not applicable (only one Phase III clinical trial for the GHIS indication is included in the NDA: trial INSM-110-303).

## **4.3 Review Strategy**

This review focuses on the efficacy and safety data presented in the clinical study report for trial INSM-110-303. The data are also analyzed in relationship to the information available in the medical literature for rhIGF-I and rhGH.

## **4.4 Data Quality and Integrity**

There was no DSI audit or investigation. The data submitted appeared complete and internally consistent.

## **4.5 Compliance with Good Clinical Practices**

The applicant states that the study protocol and its amendments were submitted for review and approval to independent ethics committees and/or institutional review boards. The applicant also states that written informed assent /consent for the study were obtained from all subjects and their parents/guardians. In addition the applicant also states that

[the] study was designed and conducted in accordance with the ethical principles described in the Declaration of Helsinki and was performed according to the Guidelines for Good Clinical Practice. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted.

## **4.6 Financial Disclosures**

The applicant submitted an FDA form 3454 in which it is stated that there was no financial agreement between Insmad and the clinical investigators “whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a).” In addition, the applicant certifies that the investigators did not have any proprietary interests or significant equity in the product as defined in 21 CFR 54.2(b) and none was a recipient of “significant payments of other sorts” as defined in 21 CFR 54.2. A list with all investigators is provided along with signed statements by each investigator supporting applicant’s statements.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

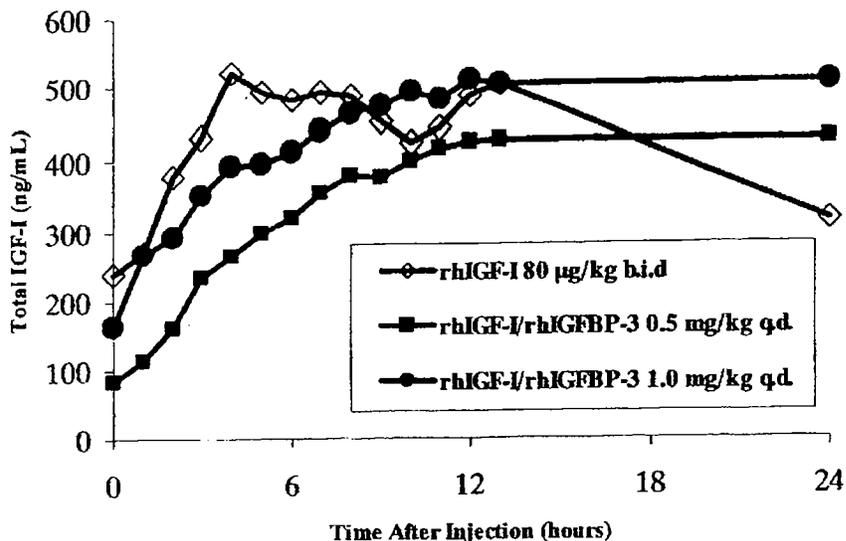
The PK characteristics for several rhIGF-I/rhIGFBP-3 doses (0.5 to 2 mg/kg) alongside a rhIGF-I dose of 80 µg/kg are summarized in Table 3 of the pharmacology review ( Dr.Jim Wei). The data are obtained from a small group of patients with GHIS.

**Table 3. Summary of pharmacokinetic parameters for IGF-I (baseline corrected)**

PK parameters	IGF-I		rhIGF/rhIGFBP3	
	Dose level			
	80 µg/kg BID	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Daily dose	160 µg/kg	105.1 ug/ml	210.2 ug/ml	420.5 ug/kg
Predose Conc. (ng/mL)	163 (114) (N=4)	0.0 (0.0) (N=4)	63 (66) (N=5)	3.1 (4.4) (N=2)
C <sub>max</sub> (ng/mL)	451 (112) (N=4)	374 (119) (N=4)	459 (131) (N=5)	352 (-) (N=2)
T <sub>max</sub> (h)	8.0 (5.8) (N=4)	19 (8.3) (N=4)	17 (7) (N=5)	21 (-) (N=2)
AUC 0-24 (ng*hr/mL)	8155 (2191) (N=4)	6645 (2278) (N=4)	8184 (2501) (N=5)	6610 (-) (N=2)
AUC 0-last (ng*hr/mL)	8155(2191) (N=4)	16630 (7570) (N=4)	10208 (3672) (N=5)	17958 (-) (N=2)
AUC 0-∞ (ng*hr/mL)	8155 (2191) (N=4)	19275 (9894) (N=4)	19076 (-) (N=2)	22912 (-) (N=2)
Half-Life (h)	-	21.1 (4.2) (N=4)	24.5 (-) (N=1)	26.9 (-) (N=2)
V <sub>z</sub> /F (L/kg)	-	0.210 (0.13) (N=4)	0.389 (-) (N=1)	0.708 (-) (N=2)
Cl/F (L/h/kg)	0.0206 (0.0048) (N=4)	0.0074 (0.0055) (N=4)	0.0110 (-) (N=1)	0.0186 (-) (N=2)

The relationship between the 0.5-1 mg/kg of rhIGF-I/rhIGFBP-3 dose and that of 80 µg/kg of rhIGF-I dose is graphically depicted in Figure 1, below (rhIGF-I has been shown to be safe and effective for doses ranging between 80 and 120 µg/kg twice a day). The IGF-I exposure for the 80 µg/kg dose of rhIGF-I is within the range of exposure for the 0.5 mg/kg to 1.0 mg/kg rhIGF-I/rhIGFBP-3 doses.

**Figure 1. Mean total serum IGF-I levels following subcutaneous injections of 80 µg/kg rhIGF-I BID 0.5 mg/kg rhIGF-I/rhIGFBP-3 and 1.0 mg/kg rhIGF-I/rhIGFBP-3**



During clinical trial INSM-110-303, IGF-I and IGFBP-3 serum concentrations were measured at baseline and Months 1, 3, 6, 9 and 12 for Cohort # 1, and Months 1, 3, and 6 for Cohort # 2, respectively.

### Cohort # 1

Mean IGF-I and IGFBP-3 serum concentrations and the mean change from baseline for these parameters are presented in Table 1. The table highlights IGF-I and IGFBP-3 measurements at around 18 hours post dose administration. Data are presented as standard deviation scores. It should be remembered that the rhIGF-I/rhIGFBP-3 dose was held relatively constant in Cohort # 1. The mean IGF-I levels peaked at Month 9 (SDS = 2.6) and subsequently decreased by Month 12 (SDS = 1.0). As the range of values indicates, the IGF-I SDS could reach remarkable levels on treatment: 23.2 and 19.4 at Months 9 and 12 respectively.<sup>35</sup> The applicant notes that the increase in mean IGF-I serum levels over time cannot be explained by the known pharmacokinetics of IGF-I and proposes that “one possible explanation could be that antibody complexes sustain rhIGF-I and rhIGF-I/rhIGFBP-3 in the serum (i.e., reduced clearance).” A post-hoc analysis indicates that there is a statistically significant correlation between antibody titer and blood levels of IGF-I and IGFBP-3 at the 3 month and 6 month timepoints.<sup>36</sup> No

<sup>35</sup> The applicant notes that “two subjects, 110, and 114, who exhibited high levels of total IGF-I at Month 9, had their daily dose of rhIGF-I/rhIGFBP-3 down-titrated prior to their 12-month visit. Subject 114 demonstrated a subsequent reduction of total IGF-I at month 12 within normal ranges. The serum level of total IGF-I in Subject 110 at 12 months was lower than the 9 month sample, but was still considerably higher than other subjects. Subject 104 had dose down-titrated after the 12-month visit.”

<sup>36</sup> The analysis is very similar with and without the outlier values contributed by subject 110.

statistical significance was observed at the Month 9 and Month 12 timepoints. In view of this finding the applicant measured free IGF-I in serum samples obtained from 12 patients at Month 12; the percentage of free IGF-I was between 0.1 and 0.6, less than that observed in the normal human serum (which was measured at 2.6 % in this evaluation and < 1% in the published literature). This suggests that the increase in IGF-I is not accompanied by excessive serum free IGF-I. A visual inspection of Appendix 16.2.8.10 by this reviewer identified the following IGF-I SDS measurements > 2: patient 7301-110 (who had all measurements >2 following the Month 3 visit (range of measurements between — , patient 7401-119 who had at the Month 3 visit all measurements between — ; patient 7901-104 who had an isolated measurement of — at Month 9; patient 8501-116 who had an isolated measurement of — at Month 9; patient 8804-114 who had multiple high measurements (most less than 2.8, one as high as — at the Month 3-9 visits. Almost all IGFBP-3 measurements done were ≤ 2.<sup>37</sup>

**Table 1: Summary of IGF-I and IGFBP-3 SDS in Cohort # 1 (Safety Population)**

Variable	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12
<b>IGF-I SDS</b>						
n	19	17	18	16	16	13
Mean (SD)	-2.5 (0.26)	-1.7 (0.79)	-0.8 (1.62)	-0.3 (2.35)	2.6 (6.42)	1.0 (5.64)
Median	-2.6	-1.9	-1.4	-0.9	0.3	-0.9
Range						
<b>IGF-I SDS change from baseline</b>						
n	NA	17	18	16	16	13
Mean (SD)	NA	0.9 (0.66)	1.7 (1.62)	2.2 (2.45)	5.2 (6.35)	3.5 (5.5)
Median	NA	0.7	1.0	1.5	3.0	1.8
Range	NA					
<b>IGFBP-3 SDS</b>						
n	19	17	18	16	16	13
Mean (SD)	-5.8 (2.53)	-5.0 (1.78)	-2.9 (2.31)	-2.4 (1.92)	-2.7 (1.95)	-2.9 (1.84)
Median	-5.7	-5.3	-3.0	-2.6	-3.1	-3.6
Range						
<b>IGFBP-3 SDS change from baseline</b>						
n	NA	17	18	16	16	13
Mean (SD)	NA	1.1 (1.63)	2.7 (2.17)	3.7 (2.29)	3.4 (2.43)	3.5 (1.54)
Median	NA	1.1	3.2	3.9	3.7	3.3
Range	NA					

Source: Appendix 14.3.4.12 – Cohort 1  
 NA = not applicable. N = number. SD = standard deviation.

## Cohort # 2

The mean IGF-I and IGFBP-3 serum concentrations and the mean change from baseline are presented in Table 2. The Table highlights IGF-I and IGFBP-3 measurements at around 18

<sup>37</sup> Patient 7401-119 had two measurements of — respectively at the Month 3 visit.

hours post dose administration. Data are presented as standard deviation scores. It should be remembered that the rhIGF-I/rhIGFBP-3 dose was titrated up to 2 mg/kg in this cohort. The mean IGF-I levels increased with each measurement until Month 6 (SDS = -0.8). The applicant notes (as in Cohort # 1) that “the increase in serum levels from Month 3 to Month 6 cannot be explained by the observed pharmacokinetics of IGF-I and IGFBP-3 following a single dose.” As noted in Cohort # 1, there was a statistically significant correlation between antibody titer to rhIGF-I/rhIGFBP-3 and serum IGF-I and serum IGFBP-3 values at Month 6 (but not at Month 3). A visual inspection of Appendix 16.2.8.10 by this reviewer identified only one IGF-I SDS measurement > 2.<sup>38</sup> All IGFBP-3 measurements done were ≤ 2.

**Table 2: Summary of IGF-I and IGFBP-3 SDS in Cohort # 2 (Safety Population)**

Variable	Baseline	Month 1	Month 3	Month 6
<b>IGF-I SDS</b>				
n	10	10	10	9
Mean (SD)	-2.6 (0.23)	-2.1 (0.37)	-1.8 (0.47)	-0.8 (1.23)
Median	-2.6	-2.2	-1.8	-1.0
Range				
<b>IGF-I SDS change from baseline</b>				
n	NA	10	10	9
Mean (SD)		0.5 (0.17)	0.8 (0.40)	1.9 (1.09)
Median		0.5	0.9	1.8
Range				
<b>IGFBP-3 SDS</b>				
n	10	10	10	9
Mean (SD)	-7.0 (1.66)	-5.8 (0.86)	-5.1 (0.95)	-3.5 (1.60)
Median	-7.5	-5.9	-5.2	-3.3
Range				
<b>IGFBP-3 SDS change from baseline</b>				
n	NA	10	10	9
Mean (SD)		1.2 (1.47)	1.9 (1.82)	3.2 (2.02)
Median		1.0	1.8	3.1
Range				

Source: Appendix 14.3.4.12 – Cohort 2

NA = not applicable. N = number. SD = standard deviation.

## 5.2 Pharmacodynamics

The main pharmacodynamic parameter for IGF-I is hypoglycemia (IGF-I, due to its ability to bind the insulin receptor with a lower affinity than insulin itself has < 10% of the glucose-lowering effect of insulin). Hypoglycemia is evaluated as a safety parameter and not as a pharmacodynamic endpoint.

<sup>38</sup> Patient 9301-203 had an IGF-I SDS of — at 12-hours during the Month 6 visit.

## Study design and patient population

The study is a prospective, open-label, multicenter, single-arm, baseline-controlled, clinical trial<sup>39</sup> conducted in 17 centers in Europe, Australia, Asia, and South America.<sup>40</sup> The patient population consists of pre-pubertal children with severe GHIS (primarily Laron Syndrome).

The study has used two drug products manufactured at two different facilities: a development scale drug product (with an API<sup>41</sup> was manufactured in Santa Clara, CA) and a commercial scale drug product (API manufactured at Avecia, in Billingham, UK).<sup>42</sup> The two above-mentioned drug products were used in two distinct cohorts of patients:

- Cohort #1, which includes 19 patients who received the development drug product for 12 months.
- Cohort # 2, which includes 10 patients who received what was supposed to be the commercial (“Avecia”) drug product for 6 months.<sup>43</sup>

As plans to use the “Avecia” manufacturing site were changed after the NDA was submitted, the applicant began manufacturing the to-be-marketed drug product at a new facility at Boulder, Colorado.

During clinical trial INSM-101-303 patients were to receive rhIGF-I/rhIGFBP-3 at either 1 or 2 mg/kg given as a subcutaneous injection once daily following the evening meal. There was no randomization to any of the two regimens. Treatment was initiated in an inpatient setting over 4 days at 0.5 mg/kg/day (Days 1 and 2), followed by a 1 mg/kg/day dose (Days 3 and 4); the purpose of the drug titration was to reduce the risk of hypoglycemia. After being discharged home patients continued rhIGF-I/rhIGFBP-3 at 1 mg/kg/day for at least 12 months in Cohort #1. For Cohort # 2 the 1 mg/kg/day regimen was given for the first 2 months followed by further titration to 2.0 mg/kg daily. Injection sites were to be rotated and the dose was recalculated and adjusted periodically to account for changes in weight. Subjects could be removed from the study for the following reasons: poor tolerability to the study drug; poor compliance (< 75% compliant with the study drug), clinically significant laboratory abnormalities, subject’s or investigator’s decision. A Steering Committee evaluated each subject’s eligibility, reviewed the

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<sup>39</sup> The study has no control group. Efficacy endpoints (such as height velocity) are compared with baseline values. It is important to recognize that the natural history of Laron Syndrome is well documented and patients who are diagnosed appropriately are not expected to have spontaneous growth acceleration. The study, which is ongoing, plans to enroll 60 patients who will be treated for 24 months.

<sup>40</sup> Each center contributed between 1 and 5 patients; most centers enrolled one patient; five centers enrolled two patients each; two other centers enrolled 4 patients and five patients each, respectively.

<sup>41</sup> API is active pharmaceutical ingredient.

<sup>42</sup> A third commercial scale drug product will have an API manufactured at Insmad Therapeutics in Boulder, Colorado. The applicant plans to use the “Boulder” drug product in another group of patients (“Cohort # 3”). No data from this cohort are presented in this NDA submission.

<sup>43</sup> A pharmacokinetic sub-study was conducted in a subset of subjects from this cohort

efficacy and safety data as it accumulated during the trial and recommended dose adjustments.<sup>44</sup> The Steering Committee could also grant waivers to inclusion/exclusion criteria.

### Inclusion criteria

The inclusion criteria were the following:

- a diagnosis of GHIS (mostly Laron Syndrome)<sup>45</sup>
- age between 2 and 18 years
- height standard deviation score (SDS)  $\leq -3$  SD
- basal serum IGF-I SDS  $\leq -2$  SD
- basal serum IGFBP-3 SDS (for age only)  $\leq -1$
- peak stimulated GH  $> 13.3$   $\mu\text{g/L}$
- pre-pubertal development<sup>46</sup>
- documented height velocity for previous 12-month period
- informed consent/assent

### Exclusion criteria

Patients were excluded for any of the following reasons: signs of puberty; prior treatment with rhIGF-I (within 3 years), GH (within 6 months), GnRH analogs, or systemic corticosteroids; malignancy; diabetes mellitus; clinically significant neuropathy, nephropathy, retinopathy, or other microvascular/macrovacular disease; abnormal renal function (serum creatinine  $> 1.7$  mg/dL).

### Protocol amendments

There were four amendments to the protocol (the first two were made, reportedly, before study initiation). They are summarized in Table 3:

**Table 3: Protocol amendments to Study INSM-110-303**

Amendment number	Amendment date	Changes
1	May 5, 2003	<ul style="list-style-type: none"><li>• changed the dosing time from breakfast to evening meal</li></ul>
2	June 30, 2003	<ul style="list-style-type: none"><li>• lowered the height inclusion criterion from <math>-2\text{SD}</math> to <math>-3\text{SD}</math></li><li>• added safety evaluations for T4, TSH, creatinine clearance</li></ul>

<sup>44</sup> The Steering Committee based its recommendations to increase or decrease the rhIGF-I/rhIGFBP-3 dose on safety information (adverse events) IGF-I levels observed during the trial.

<sup>45</sup> If required to confirm the diagnosis, an IGF-I Generation test was done in order to show inadequate rise in IGF-I levels.

<sup>46</sup> Defined as Tanner breast stage 1 for girls or testis volume  $< 4$  mL for boys.

		<ul style="list-style-type: none"> <li>• changed the definition of the evaluable population</li> <li>• eliminated the ITT efficacy analysis</li> <li>• changed the dose groups for analysis (1 mg/kg/day versus 2 mg/kg/day)</li> <li>• changed the primary analysis to include the first 15 evaluable patients with 6 months of dosing</li> <li>• introduced a protocol addendum for the Pharmacokinetic Substudy</li> </ul>
3	Dec. 17, 2003	<ul style="list-style-type: none"> <li>• changed from a patient allocation to two dosing regimens (1 mg/kg and 2 mg/kg) to a titration to tolerability (1 mg/kg initially then 2 mg/kg)</li> <li>• added safety assessments (echocardiograms, audiograms) and enhanced the evaluation of hypoglycemia</li> <li>• made changes to the PK substudy</li> </ul>
4	Sept. 22, 2004	<ul style="list-style-type: none"> <li>• increased the number of patients to be enrolled from 40 to 60</li> <li>• added a 12-month extension to the 12-month original study</li> <li>• added safety evaluations (testosterone and estradiol levels, uterine and ovarian ultrasounds)</li> <li>• added predicted adult height as a secondary endpoint</li> <li>• limited the dose of rhIGF-I/IGFBP-3 to 1 mg/kg for Cohort # 1 during the first 12 months of study</li> </ul>

Source: text in Volume 12, Section 5.3.5.1.1

### Efficacy assessments and statistical analysis plan

Efficacy assessments were mostly related to linear growth. They included standing height,<sup>47</sup> sitting height, weight, head circumference, pubertal stage, and bone age (used for calculation of predicted adult height).

The primary efficacy analysis was the change in height velocity (expressed as cm/yr) on treatment relative to pre-treatment height velocity. The secondary efficacy analyses were related to changes in several auxologic measurements (standing height, sitting height, weight and head circumference), BMI, pubertal stage, bone age and predicted adult height.<sup>48</sup>

<sup>47</sup> Standing height was measured at baseline, Month 1, and every 3 months post-baseline and was used to calculate the primary efficacy endpoint (height velocity). Baseline height information was obtained from “heights recorded during the 12-month period prior to entry into the study.” The applicant states that “for consistency, standing height measurements were, to the extent possible, taken at each study visit by the same observer, using the same stadiometer at the same time of day.”

<sup>48</sup> Bone age, using x-ray of left hand and wrist, was determined at screening and every six months post-baseline, and analyzed centrally (Professor [redacted], using the Tanner-Whitehouse (TW2) RUS maturity score (or bone age). If, for a single subject, more than one bone age reading was provided for a given date, the results were averaged.

Due to the variability inherent in assessments of skeletal maturation, a second central reading was performed at the [redacted] using the FELS Method. Predicted adult height was calculated at baseline and every 6 months thereafter according to the 3-variate equation from the Tanner-Whitehouse Mark II system (TW II), in which predicted adult height is calculated using the subject’s height, chronological age, and bone age. A second adult height prediction was calculated using the subject’s height, chronological age, and bone age and the Bayley-Pinneau predicted adult height method; this method provides height predictions for children with bone ages > 6 yr.

The applicant defines the safety population as “all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment.” The efficacy evaluable population included subjects who met several selected inclusion criteria,<sup>49</sup> were not major protocol violators, were at least 80% compliant with study dosing, had received study medication for at least 159 days (for the 6-month efficacy evaluable population) or 330 days (for the 12-month efficacy evaluable population) and had efficacy measurements at Month 6 or 12, respectively.

### Disposition of patients

Of the 29 subjects enrolled in the study at the time of the NDA admission, 19 were in Cohort #1 and 10 were in Cohort # 2.

#### Cohort # 1

Of the 19 subjects enrolled in Cohort # 1, all 19 (100%) are included in the safety population; 16 (84%) are included in the efficacy evaluable population at Month 6 and Month 12, respectively. The three patients who were not included in the efficacy analyses were:

- subject 7601-107: discontinued the study at Month 5 due to a series of serious adverse events (and subsequent death)
- subject 7801-103: was lost for follow-up at Month 3
- subject 7401-119: discontinued temporarily treatment for a prolonged period of time because of an ovarian cyst and had less than the minimally required exposure to study drug.

Subject disposition for Cohort # 1 is summarized in Table 4.

**Table 4: Subject Disposition, Cohort # 1**

	No. Subjects
<b>Enrolled</b>	19 (100 %)
<b>Continue in trial to date</b>	17 (89%)
<b>Discontinued</b>	2 (11 %)
<b>Discontinued for adverse event</b>	1 (5 %)
<b>Lost for follow up</b>	1 (5 %)

\* Source: Table 5 of Clinical Study Report, Cohort # 1, Report #2

#### Cohort # 2

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<sup>49</sup> They included: documented height velocity from previous 12-month period, diagnosis of GHIS, such as Laron syndrome, prepubertal status, height SDS < -2 for subjects enrolling prior to implementation of the 30 June 2003 protocol amendment or height SDS ≤ -3 for subjects enrolling after implementation of the 30 June 2003 protocol amendment.

Of the 10 subjects enrolled in Cohort # 2 all 10 subjects are included in the safety population for this cohort. Nine of them (90%) are included in the efficacy population at 6 months.<sup>50</sup> There was one patient discontinuation reported to date in Cohort # 2 for poor compliance.

## Dosing

The rhIGF-I/rhIGFBP-3 dose evaluated in Cohort # 1 was 1.0 mg/kg/day (downward dose adjustment was allowed for safety reasons). All but two subjects were titrated to the 1.0 mg/kg/day dose.<sup>51</sup>

A higher dose (2.0 mg/kg/day) was evaluated in Cohort # 2. Protocol amendment # 3 allowed dose titration up to a maximum of 2.0 mg/kg daily according to the algorithm described below. All patients were finally titrated to the 2.0 mg/kg/day dose.<sup>52</sup>

IGF-I SDS	Daily Dose Adjustment (maximum daily dose: 2.0 mg/kg):
< -2	Increase dose by 1.0 mg/kg/day
-2 to 0	Increase dose by 0.5 mg/kg/day
0 to +3	No change
> +3	Decrease dose 0.5 mg/kg/day

Source: text.

## Protocol violations and deviations

### Cohort # 1

The applicant lists the following protocol violations and deviations for Cohort # 1:

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<sup>50</sup> Subject 8301-211 has not completed the 6-month visit and received <159 days of treatment and therefore is not included in the efficacy evaluable population; this subject discontinued the drug for approximately one and one-half month because of elevated transaminases at Month 3.

<sup>51</sup> Subjects 7301-110 and 8804-114 had their doses decreased to 0.5 mg/kg daily due to excessive IGF-I levels; these dose reductions occurred at approximately Months 12 and 11, respectively. In addition, subject 8802-112 had approximately 4 weeks of reduced dosing to 0.5 mg/kg following a hypoglycemic episode.

<sup>52</sup> Based on IGF-I SDS values obtained at Month 1, four subjects had their dose increased to 1.5 mg/kg daily and six subjects had their dose increased to 2.0 mg/kg daily, all after 2 to 3 months on treatment. Based on IGF-I SDS values obtained at Month 3, three of the 4 subjects receiving 1.5 mg/kg daily increased the dose to 2.0 mg/kg daily at approximately Month 5. The fourth of these subjects increased his dose to 2.0 mg/kg daily at Month 6, after normalization of transaminase levels.

- Four subjects did not have GH stimulation test performed (two of them had, reportedly, GH gene deletion).
- Two subjects (see also the Disposition of Patients paragraph) were not included in the evaluable population.<sup>53</sup>
- Two subjects (7501-105 and 7502-105) initiated treatment at 1 mg/kg dose instead of 0.5 mg/kg dose.
- Subject 7301-110 did not participate in the in-patient phase of the study and initiated treatment at a dose of 1.0 mg/kg daily.
- Two other subjects (7201-117 and 7202-118) did not have height measurements at the start of the treatment; the applicant used height data obtained at screening (3 weeks prior to treatment initiation).
- Subject 8202-102 missed doses sporadically for intercurrent illnesses.
- Subject 7301-110 missed several days of treatment on two occasions due to holiday.
- Subject 7401-119 missed 123 days of study medication due to an adverse event (ovarian cyst)<sup>54</sup> and Subject 7201-117 missed 17 days of treatment due to failure to pick up study medication.
- Subject 8802-112 had approximately 4 weeks of reduced dosing to 0.5 mg/kg following a hypoglycemic episode.
- Two subjects, 7301-110 and 8804-114 had an average daily dose of 0.9 mg/kg during the first 12 months of treatment on account of missed doses or dosing change.
- 14 subjects did not have echocardiograms and 18 patients did not have audiograms prior to the first dose; instead, “assessments were obtained in most subjects shortly after implementation of the amendment;” this protocol deviation was reportedly due to the lack of implementation of Protocol Amendment # 3 at all sites.

With the exception of the two subjects who lacked baseline GH stimulation and did not have GH gene deletion and thus could not formally be ruled out as having growth hormone deficiency, all the other violations and deviations were relatively minor and could not introduce bias in the efficacy analyses. The applicant states that the “reasons for this [lack of GH stimulation testing] were reviewed and accepted by the Steering Committee.”

## Cohort # 2

The applicant reports the following protocol violations and deviations for Cohort # 2:

- Five subjects did not have an IGFBP-3 measurement at the time of the screening visit; however, the subjects’ IGFBP-3 levels have been measured within the study and, reportedly, satisfied the inclusion criterion.
- Five subjects (7701-201, 9302-204, 9401-207, 8806-208, and 9101-210) missed 1-10 doses of the study drug, “generally for intercurrent illnesses.”

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<sup>53</sup> Subject 7601-107 had inaccurate standing heights, as he was not compliant with the measuring procedure; he died 5 months after enrollment. Subject 7801-103 was lost for follow-up at 3 months.

<sup>54</sup> This subject did not meet the criteria of inclusion in the efficacy evaluable population.

- One subject (8301-211) discontinued the study drug for approximately one and one-half months due to elevated transaminases at Month 3.<sup>55</sup>

All of the above-described violations and deviations for Cohort # 2 were minor and inconsequential.

## Compliance

### Cohort # 1

For Cohort # 1, the applicant reports a mean compliance at 12 months of treatment of 99.1%. Compliance was 100% in 7/18 (37%) subjects, 90-99% in 11/18 (58%) of subjects; one subject did not complete the 12 month visit at the time the study report.

### Cohort # 2

In Cohort # 2, the applicant reports that overall compliance with study medication was 98.6%. Four out of 9 subjects had 100% compliance and 5/9 subjects had 90 - 99% compliance.<sup>56</sup> One patient who has not yet completed the 6-month study visit and is reported to have withdrawn.

## Demographics and baseline characteristics

The demographics and baseline characteristics for the safety populations (Cohort # 1 and # 2 as well as for the two cohorts combined) are displayed in Table 5. Overall, the most common cause of GHIS was Laron Syndrome (93 % of all patients); only 2 (7 %) patients in Cohort # 1 had GH gene deletion. At the time of enrollment patients were extremely short (mean height SDS of -7.0), had a reduced height velocity (mean HV: 2.9 cm per year), had an average chronological age of 8.4 years with a delayed mean bone age (5.9 years), and were all prepubertal. Baseline IGF-I SD scores and IGFBP-3 SD scores were also low (mean values of -2.6 and -6.2, respectively). The baseline characteristics are typical of patients with severe GHIS.

**Table 5: Demographics and Baseline Characteristics**

Variable	Cohort # 1 Safety Population (n=19)	Cohort # 2 Safety Population (n=10)	All Cohorts (n=29)
GHIS Diagnosis (n,%)			
GH Receptor Deficiency	17 (89.5%)	10 (100%)	27 (93%)
GH Gene Deletion	2 (10.5%)	0 (0%)	2 (7%)

<sup>55</sup> This patient was excluded from the efficacy evaluable population.

<sup>56</sup> Specifically, subject 7701-201 missed two doses unintentionally; subject 9302-204 missed 6 doses for upper respiratory tract infection and hypoglycemia; subject 8806-208 temporarily interrupted treatment at the Month 1 visit for 10 days due to elevated transaminases; subject 9401-207 missed 3 doses for intercurrent illness; subject 9101-210 missed one dose due to hypoglycemia; subject 8301-211 discontinued study drug for approximately one and one-half months due to elevated transaminases at Month 3.

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 {Mecasermin rinfabate (iPLEX)}

Gender (n,%)			
Male	13 (68%)	4 (40%)	17 (59%)
Female	6 (32%)	6 (60%)	12 (41%)
Race (n,%)			
Caucasian	13 (68%)	9 (90%)	22 (76%)
Black	0 (0%)	0 (0%)	0 (0%)
Asian	6 (32%)	0 (0%)	6 (21%)
Other	0 (0%)	1 (10%)	1 (3%)
Pubertal Stage (n,%)	19 (100%)	10 (100%)	29 (100%)
Age (yr)			
n	19	10	29
Mean ± SD	8.4 ± 2.9	8.6 ± 3.9	8.4 ± 3.2
Median	8.0	7.6	8.0
Range	3.1 - 14.8	3.3 - 14.6	3.1 - 14.8
Bone age (yr)			
n	17	10	27
Mean ± SD	6.45 ± 3.3	4.9 ± 2.7	5.9 ± 3.2
Median	5.8	4.2	5.7
Range	1.6 - 12.6	1.8 - 8.7	1.6 - 12.5
Height SDS			
n	19	10	29
Mean ± SD	-6.4 ± 1.9	-8.0 ± 1.1	-7.0 ± 1.8
Median	-6.2	-8.3	-7.1
Range	-10.0 - -2.8	-9.3 - -6.1	-10.0 - -2.8
Target (mid-parental) Height SDS			
n	19	8	27
Mean ± SD	-1.2 ± 0.5	-1.3 ± 0.5	-1.2 ± 0.5
Median	-1.2	-1.2	-1.2
Range	-1.9 - 0	-2.2 - -0.5	-2.2 - 0
Predicted Adult Height SDS			
n	14	8	22
Mean ± SD	-5.3 ± 1.5	-5.7 ± 1.4	-5.4 ± 1.5
Median	-5.3	-5.5	-5.5
Range	-9.0 - -3.4	-8.5 - -3.6	-9.0 - -3.4
Height Velocity (cm/yr)			
n	19	10	29
Mean ± SD	3.4 ± 1.8	2.1 ± 1.5	2.9 ± 1.8
Median	3.2	1.9	2.9
Range	0.3 - 7.5	0.2 - 4.1	0.2 - 7.5
Weight (kg)			
n	19	10	29
Mean ± SD	15.9 ± 8.0	10.9 ± 2.4	14.2 ± 7.0
Median	13.4	10.7	11.3
Range	7.5 - 33.9	7.6 - 16.0	7.5 - 33.9
IGF-I SDS			
n	19	10	29
Mean ± SD	-2.5 ± 0.3	-2.6 ± 0.2	-2.6 ± 0.2
Median	-2.6	-2.6	-2.6
Range	-2.8 - -2.0	-2.9 - -2.2	-2.9 - -2.0
IGFBP-3 SDS			
n	19	10	29

Clinical Review  
 {Dragos Roman}  
 {21-884/N000}  
 {Mecasermin rinfabate (iPLEX)}

Mean ± SD	-5.8 ± 2.5	-7.0 ± 1.7	-6.2 ± 2.3
Median	-5.7	-7.5	-5.9
Range	-10.1 - -1.5	-9.9 - -5.0	-10.1 - -1.5

Source: Table 6 from Clinical Study Report (Cohort # 2, Report # 2).

## 6.1.4 Efficacy Findings

### Cohort # 1

#### Primary efficacy analysis

The primary efficacy analysis was the change in height velocity (HV) during treatment relative to pre-treatment height velocity. The annualized pre-treatment height velocity for the efficacy evaluable population (16 subjects) was  $3.4 \pm 1.9$  (mean  $\pm$  SD) cm/yr.<sup>57</sup> During treatment with rhIGF-I/rhIGFBP-3 it increased to  $7.4 \pm 2.0$  cm/yr for Months 0-6 ( $p < 0.0001$  compared to pre-treatment HV) and  $6.4 \pm 1.6$  cm/yr for Month 0-12 ( $p = 0.0018$  compared to pre-treatment HV). These results are summarized in applicant's Table 7. The mean change in height velocity from pre-treatment to Months 0-6 was  $4.0 \pm 1.8$  cm/yr (range: 2.1 to 7.5 cm/yr); from pre-treatment to Months 0-12 it was  $3.0 \pm 1.3$  cm/yr (range: 1.0 to 5.1 cm/yr; 95% C.I. = 2.3-3.7 cm/yr).<sup>58</sup>

For the two subjects with GH gene deletion and antibodies to GH the height velocities for Months 0-12 were — cm/yr and the HV changes from baseline were — :m/yr, respectively. These results were comparable with those observed for the whole group of subjects.

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<sup>57</sup> 9/16 (56%) subjects had a pre-treatment height velocity of 3 cm/yr or less.

<sup>58</sup> Three patients did not meet the pre-defined criteria to be included in the efficacy evaluable population. To examine the effects of eliminating these three subjects from the primary efficacy analysis the applicant conducted a sensitivity analysis in which the missing heights (and missing height velocities) were estimated conservatively by applying pretreatment values. This analysis was conducted for all enrolled subjects ( $n = 19$ ) and resulted in a mean height velocity for Months 0-6 of  $7.0 \pm 2.5$  cm/yr and for Months 0-12 of  $6.0 \pm 2.0$  cm/yr. The change in height velocity from pretreatment was  $3.6 \pm 2.1$  and  $2.7 \pm 1.6$  cm/yr, respectively for the periods analyzed ( $p < 0.0001$  for either change from baseline). These results were comparable to the results for the evaluable population. It is also important to note that all subjects remained pre-pubertal during this treatment period.

**Table 7. Height Velocity (cm/yr) in Efficacy Evaluable Population (n=16)**

	Pre-Treatment	Months 0-6	Months 0-12	Change Pre-Tx to Mo 0-6	Change Pre-Tx to Mo 0-12
Height Velocity (cm/yr)					
Mean	3.4	7.4	6.4	4.0	3.0
SD	1.9	2.0	1.6	1.8	1.3
SE	0.5	0.5	0.4	0.5	0.3
Median	3.1	7.1	6.0	3.1	3.1
Minimum					
Maximum					
p-value				<0.0001 <sup>1</sup>	<0.0018 <sup>2</sup>

<sup>1</sup> Wilcoxon signed rank test

<sup>2</sup> Paired t-test

The individual height velocity responses on treatment are displayed in applicant's Figure 2. All patients were responders to treatment in that all patients appear to have an increase in HV relative to baseline. The increase in height velocity from pre-treatment to Months 0-6 was at least 2 cm/yr in 16/16 (100 %) of subjects; it was at least 4 cm/yr in 6/16 (38 %) patients. The increase in height velocity from pre-treatment to Months 0-12 was at least 2 cm/yr in 12/16 (75%) subjects and at least 4 cm/yr in 6/16 (38%) subjects. The applicant conducted several exploratory analyses which indicate that HV on treatment and change in height velocity did not correlate with age, race, baseline height SDS, mid-parental target height SDS, or predicted adult height SDS. It did correlate with baseline BMI SDS ( $r=0.62, 0.74, p=0.01, 0.0012$ , respectively,  $n=16$ ).<sup>59</sup>

**Figure 2. Individual Height Velocity in Efficacy Evaluable Populations (n=16)**



<sup>59</sup> In addition, the applicant observes that height velocity for Month 0-12 positively correlated with baseline ALS levels ( $r=0.69, p=0.0031, n=16$ ). The mean height velocity for Months 0-12 was  $7.3 \pm 1.3$  cm/yr for subjects with baseline ALS > 0 mg/L ( $n=10$ ) and  $5.0 \pm 0.5$  cm/yr for subjects with non-detectable ALS level ( $n=6$ ).

## Secondary efficacy analyses

### Height SDS

The mean baseline height SDS for the efficacy evaluable population (n=16) was  $-6.4 \pm 2.1$ .<sup>60</sup> During treatment the mean height SDS increased to  $-6.1 \pm 2.1$  at Month 6 (mean change  $0.3 \pm 0.2$ ,  $p < 0.0001$ ) and to  $-6.0 \pm 2.2$  at Month 12 (mean change  $0.5 \pm 0.4$ ,  $p = 0.0017$ ). After 12 months of therapy, the increase in height SDS was at least 0.3 in 14/16 (88%) subjects and at least 0.5 in 10/16 (63%) subjects.

### Bone age

Bone age was assessed by central readings of left hand/wrist X-rays obtained at baseline, Month 6, and Month 12. The applicant used two different measurement methods: Tanner-Whitehouse 2 RUS and FELS. The mean bone age change from baseline was  $0.3 \pm 0.5$  yr for Months 0-6 (n=15) and  $1.5 \pm 0.8$  yr for Months 0-12 (n=15) using the TW2 RUS method; it was  $0.5 \pm 0.4$  yr for Month 0-6 (n=14) and  $1.4 \pm 0.6$  yr for Months 0-12 (n=14) using the FELS method. A bone age change in excess of chronological age change is to be expected due to the delay in bone age relative to chronological age noted at baseline.

### Predicted adult height

The change in predicted adult height was calculated by two different methodologies, each corresponding to a specific method of measurement of the bone age: Tanner-Whitehouse Mark II (TW II) and Bayley-Pinneau, respectively. The predicted adult height SDS change from baseline to Month 12, using the TW II method, was  $0.2 \pm 0.4$  ( $p = 0.1254$ , n=14); for the Bayley-Pinneau method the change in predicted adult height SDS was greater ( $0.5 \pm 0.3$ ;  $p = 0.0193$ , n=6). It is important to recognize that the change in predicted adult height is an exploratory analysis as none of the above-mentioned methodologies used to predict adult height has been validated in GHIS.

## Cohort # 2

### Primary efficacy analysis

The primary efficacy analysis was the change in height velocity during treatment relative to pre-treatment height velocity. The mean annualized pre-treatment height velocity for the efficacy evaluable population (n = 9) was  $2.2 \pm 1.5$  cm/yr.<sup>61</sup> During treatment with rhIGF-I/rhIGFBP-3 it increased to  $9.3 \pm 2.7$  cm/yr for Months 0-3 ( $p < 0.0001$  relative to baseline HV)

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<sup>60</sup> At baseline 15/16 (94%) subjects had baseline height SDS  $< -3$ ; one subject had baseline height SDS of  $-2.8$ .

<sup>61</sup> 6/9 (67%) had a pre-treatment height velocity of 3 cm/yr or less.

and to  $8.8 \pm 2.0$  cm/yr for Months 0-6 ( $p < 0.0001$  relative to baseline).<sup>62</sup> These results are summarized in applicant's Table 7 (from Clinical Study Report, Cohort # 2, Report # 2). The mean change in height velocity was  $7.1 \pm 2.8$  cm/yr from pre-treatment to Months 0-3, and  $6.6 \pm 2.6$  cm/yr from pre-treatment to Months 0-6 (95% CI: 4.6 to 8.6 cm/yr).<sup>63</sup>

Table 7. Height Velocity (cm/yr) for Efficacy Evaluable Subjects in Cohort #2 (n=9)

	Pre-Treatment	Months 0-3	Months 0-6	Change Pre-Tx to Mo 0-3	Change Pre-Tx to Mo 0-6
Height velocity (cm/yr)					
Mean	2.2	9.3	8.8	7.1	6.6
SD	1.5	2.7	2.0	2.8	2.6
SE	0.5	0.9	0.7	0.9	0.9
Median	2.3	9.7	9.5	6.6	7.6
Minimum					
Maximum					
p-value <sup>1</sup>				<0.0001	<0.0001

<sup>1</sup> Paired t-test

All patients had an increase in height velocity on treatment: 9/9 (100%) subjects had an increase of at least 2 cm/yr. Seven out of nine (78%) subjects had an increase in height velocity of at least 4 cm/yr, and 6/9 (67%) had an increase of at least 6 cm/yr over 6 months. The individual height velocity measurements (pre-treatment to Months 0-3 and to Month 0-6 are illustrated in applicant' Figure 2.<sup>64</sup>

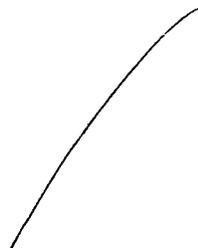
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<sup>62</sup> In Cohort # 2 the dose of study drug was 1 mg/kg for the first two months and was titrated to 2 mg/kg/day for all patients.

<sup>63</sup> One patient did not meet the pre-defined criteria to be included in the efficacy evaluable population. To examine the effects of eliminating this subject from the primary efficacy analysis the applicant conducted a sensitivity analysis in which the missing height (and missing height velocity) was estimated conservatively by applying pretreatment values. This post-hoc sensitivity analysis for all enrolled subjects in Cohort #2 (n=10) resulted in a mean pre-treatment height velocity of  $2.1 \pm 1.5$  cm/yr, a Month 0-6 HV of  $8.2 \pm 2.7$  cm/yr, and a change in HV from pretreatment of  $6.1 \pm 3.0$  cm/yr ( $p < 0.0001$ , t-test). These results were comparable to the results for the evaluable population.

<sup>64</sup> Height velocity for Months 0-6 did not correlate with pre-treatment height velocity, baseline age, baseline height SDS, baseline BMI SDS, mid-parental target height SDS, or predicted adult height SDS.

**Figure 2. Individual Height Velocity in Efficacy Evaluable Subjects in Cohort #2 (n=9)**



## Secondary efficacy analyses

### Height SDS

The mean baseline height SDS for Cohort # 2 was  $-7.9 \pm 1.1$  (n=9).<sup>65</sup> During treatment with rhIGF-I/rhIGFBP-3 the mean height SDS increased to  $-7.5 \pm 1.1$  at Month 6 (the mean change in height SDS for this timepoint was  $0.42 \pm 0.25$ ;  $p=0.0009$  versus baseline). Eight out of nine (89%) patients had an increase in height SDS of at least 0.1; 6/9 (67%) subjects had an increase in height SDS of at least 0.3, and 4/9 (44%) had an increase in height SDS of at least 0.5.

### Bone age

Measurements of the mean bone age indicate that it advanced  $1.1 \pm 0.4$  yr by the TW2 RUS method and  $0.7 \pm 0.4$  yr by the FELS Method (n=7 for both) for a 6-month time interval.

### Predicted adult height

The mean change in predicted adult height SDS from baseline to Month 6 was  $0.16 \pm 0.44$  ( $p=0.4179$ , n=6) using the TW II method and  $0.34 \pm 0.11$  ( $p=0.032$ , n=3) using the Bayley-Pinneau method.<sup>66</sup>

### Efficacy comparisons between Cohort # 1 and Cohort # 2

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<sup>65</sup> All subjects in this cohort had baseline height SDS  $< -3$ .

<sup>66</sup> The Bayley-Pinneau is not applicable to subjects with bone age  $< 6$  yr. None of the two methodologies has been validated in children with GHIS.

Twenty-five (86%) of the 29 subjects enrolled in Cohorts #1 and Cohort #2, were evaluable for efficacy at six months. The two cohorts shared many similarities in baseline characteristics but also displayed some differences in baseline height velocity and height SDS; specifically, patients in Cohort # 2 were shorter (height SDS of -8.0 vs. -6.4) and had slower height velocities (2.1 cm/yr vs. 3.4 cm/yr).<sup>67</sup> Applicant's Table 9 summarizes the efficacy results for a comparable period of treatment (6 months) for Cohorts # 1 and # 2, as well as for the two cohorts combined. Study drug dose was higher in Cohort # 2 (mean daily dose of 1.4 mg/kg vs. a mean daily dose of 0.96 mg/kg in Cohort # 1). The mean height velocity was greater in Cohort #2 (8.8 cm/yr

Table 9. Comparison of Efficacy Results for Month 0-6 for Cohorts #1 and #2 (Mean ± SD)

Endpoint	Cohort #1 (n=16)	Cohort #2 (n=9)	All Cohorts (n=25)
Prescribed Dose (mg/kg daily)	Mo. 0-2: 1.0 Mo. 3-6: 1.0	Mo. 0-2: 1.0 Mo. 3-6: 1.5-2.0	Mo. 0-2: 1.0 Mo. 3-6: 1.0-2.0
Average Daily Dose (mg/kg daily)	0.96	1.4	1.1
Height Velocity (cm/yr)			
Pre-Treatment	3.4±1.9	2.2±1.5	3.0±1.8
Months 0-6	7.4±2.0	8.8±2.0	7.9±2.1
Change from Pre-Tx	4.0±1.8	6.6±2.6	5.0±2.4
p-value vs pre-Tx	<0.0001 <sup>1</sup>	<0.0001 <sup>2</sup>	<0.0001 <sup>1</sup>
Height SDS			
Baseline	-6.5±2.1	-7.9±1.1	-7.0±1.9
Months 0-6	-6.1±2.1	-7.5±1.1	-6.6±1.9
Change from Baseline	0.3±0.2	0.4±0.3	0.4±0.2
p-value vs Baseline	<0.0001 <sup>2</sup>	0.0009 <sup>2</sup>	<0.0001 <sup>2</sup>

<sup>1</sup> Wilcoxon signed rank test

<sup>2</sup> Paired t-test

versus 7.4 cm/yr), as was the change in height velocity relative to baseline (6.6 cm/yr versus 4.0 cm/yr). The mean gain in height SDS relative to baseline was slightly larger for Cohort # 2 (0.4 ± 0.3 vs. 0.3 ± 0.2 in Cohort # 1).<sup>68</sup> In the two cohorts combined the mean gain in height velocity

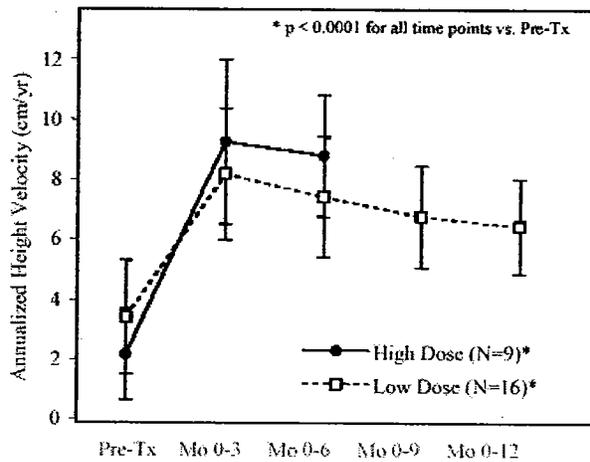
<sup>67</sup> In addition, the proportion of males was greater in Cohort #1 and females greater in Cohort #2. ALS was undetectable in 8/9 subjects in Cohort #2, compared with only 6/16 in Cohort #1. The two cohorts had comparable baseline IGF-I SDS (-2.6 for each cohort) and slightly different IGFBP-3 SDS (-5.8 for Cohort # 1 and -7.5 for Cohort # 2).

<sup>68</sup> The applicant conducted a sensitivity analysis for all subjects enrolled (n=29), in which the missing Month 6 heights was estimated conservatively based on the pre-treatment height velocities. This analysis resulted in a mean pre-treatment height velocity of 2.9±1.8 cm/yr, a Month 0-6 HV of 7.4±2.6 cm/yr, and a change in HV from pretreatment of 4.5±2.7 cm/yr (p<0.0001, t-test). These results were comparable to the results for the evaluable population. In addition, the applicant conducted an analysis of height velocity response in subgroups based on baseline ALS and dose received (low dose in Cohort #1 versus high dose in Cohort #2). The height velocity for Months 0-6 was 6.3 cm/yr in the subjects with no ALS treated with low dose, compared with 9.1 cm/yr for subjects with no ALS treated with high dose. Subjects with measurable ALS had better mean pre-treatment height velocity (4.3 cm/yr) and achieved a height velocity for Months 0-6 of 8.1 cm/yr on low dose. The applicant proposed that "these data suggest that subjects lacking ALS are more likely to require a higher dose."

from baseline to Month 6 was  $5.0 \pm 2.4$  cm/yr, with all 25 (100%) subjects demonstrating an increase of at least 2 cm/yr. The combined change in height SDS relative to baseline was  $0.4 \pm 0.2$ . The mean change in bone age was  $0.6 \pm 0.4$  years at Month 6 in the two cohorts combined by each of the bone age methods.

Applicant's Figure 4 illustrates the height velocity data for the low dose (N=16) and high dose (n=9) cohorts.

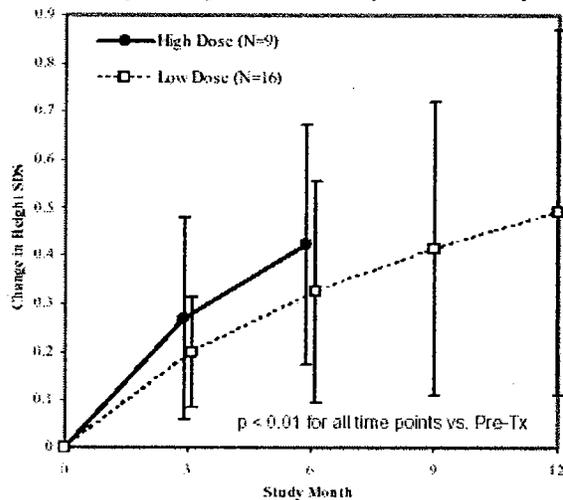
Figure 4. Height Velocity in All Cohorts Efficacy Evaluable Population by Dose (Mean  $\pm$ SD)



Applicant's Figure 7 illustrates the height SDS data for the low dose (N=16) and high dose (n=9) cohorts.

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Figure 7. Change in Height SDS in Efficacy Evaluable Subjects in all Cohorts



### 6.1.5 Clinical Microbiology

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

### 6.1.6 Efficacy Conclusions

RhIGF-1/rhIGFBP-3 was effective in increasing short-term linear growth in patients with severe growth hormone insensitivity due to either Laron syndrome or GH gene deletion and neutralizing antibodies to GH. For the 25 patients (of the 29 enrolled) who comprise the Month 6 evaluable population, rhIGF-1/rhIGFBP-3 at an average daily dose of 1.1 mg/kg more than doubled the mean height velocity from  $3.0 \pm 1.8$  cm/yr to  $7.9 \pm 2.1$  cm/yr. The change in HV relative to baseline measured  $5.0 \pm 2.4$  cm/yr and was statistically significant ( $p < 0.0001$ ).<sup>69</sup> All subjects had a HV increase of at least 2 cm/yr. For the same rhIGF-1/rhIGFBP-3 dose the height SDS change at 6 months was  $0.4 \pm 0.2$  ( $p < 0.0001$ ).

Several observations were made for two distinct cohorts of patients treated with different doses of rhIGF-1/rhIGFBP-3 for up to 6-12 months. In a cohort of 16 patients treated for 12 months with a daily mean dose of 0.96 mg/kg (development product) the mean change in HV was  $3.0 \pm 1.3$  cm/yr (range — ) and the mean change in height SDS was  $0.5 \pm 0.4$  (both changes were statistically significant relative to baseline). In a second cohort treated only for 6 months at a

<sup>69</sup> It is important to recognize that the 6-month annualized height velocity overstates the annual height velocity because catch up growth is more rapid for the first 6 months of the first year of treatment.

mean daily dose of 1.4 mg/kg (“commercial product”) the mean change in HV was  $6.6 \pm 2.6$  (range — cm/yr) and the change in height SDS was  $0.42 \pm 0.25$  (both changes were statistically significant relative to baseline). When 6 month data was compared between the “high dose” and the “low dose” cohorts the former appeared more effective (HV change from baseline of  $6.6 \pm 2.6$  cm/yr vs.  $4.0 \pm 1.8$  cm/yr). However it is very important to acknowledge that patients were not randomized but assigned to the two different dose regimens thus limiting the ability to draw firm conclusions with respect to dose response.

The changes in height velocity and height SDS did not appear to be associated with an excessive acceleration in bone age.<sup>70</sup> Predicted adult height increased with treatment but one needs to recognize the exploratory quality of this analysis since methods of height prediction have not been validated in patients with GHIS.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### 7.1.1 Deaths

##### Cohort # 1

##### Deaths

One subject (7601-107) died during the course of the study (this is the only subject who withdrew early due to an adverse event in the GHIS clinical program: hepatomegaly).<sup>71</sup> He was

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<sup>70</sup> For Cohort # 1 the mean bone age change from baseline was  $1.5 \pm 0.8$  yr and  $1.4 \pm 0.6$  (for two different methodologies employed for Months 0-12). For the commercial product (Cohort 2) data are available only for the first 6 months of treatment; the bone age change for this time interval was  $1.1 \pm 0.4$  yr and  $0.7 \pm 0.4$  yr by two different methods used.

<sup>71</sup> This patient was hospitalized after 5 months in the study for an exacerbation of chronic bronchitis. Hepatomegaly was noted a few days after the hospital admission and confirmed ultrasonographically (liver enlargement was not present on the baseline abdominal ultrasound). The study drug was discontinued. The applicant reports that there was also a “slight elevation of liver enzymes [...] at timepoints prior to, during, and after treatment with study medication.” Viral serology was consistent with prior Hepatitis B immunization and negative for cytomegalovirus, hepatitis A and C, and Epstein-Barr virus. Repeat liver ultrasound 5 days later showed regression of hepatomegaly. The subject was discharged home and, reportedly, “remained asymptomatic for any liver disease.” Subsequently, while being off study drug, the patient was hospitalized twice for obstructive bronchitis (hospital admissions were 3 weeks apart). During the second hospitalization he was also diagnosed with “possible mitral valve stenosis.” A few days after discharge he was hospitalized again for obstructive bronchitis, acute cyanosis, and difficulty breathing (later he was diagnosed with respiratory syncytial virus infection and acute interstitial pneumonia). Following worsening in dyspnea and tachycardia he was mechanically ventilated. Shortly thereafter he died due to respiratory

4.5 year-old at enrollment who had five serious adverse events during the clinical trial: 3 events of obstructive bronchitis requiring hospitalization, one event of hepatomegaly causing prolongation of hospitalization, and cardio-respiratory failure secondary to a combination of underlying heart disease (endocardial fibroelastosis) and respiratory syncytial virus infection. The investigator considered the three obstructive bronchitis adverse events and the cardiorespiratory failure adverse event not related to study drug; the hepatomegaly adverse event was assessed as possibly related. Importantly, the translated pathology report states that the heart had “massive endocardial fibroelastosis of each cavities of the heart” [...] and that “the patient has to be suffered from the endocarditis long-termed at least 9 months” [i.e. prior to the enrollment in the clinical trial]. The report concludes that the patient’s death was attributed to “a firstly respiratory failure and secondary heart failure consolidated by an long-term proceeded fibrous endocarditis.”

## **Cohort # 2**

There were no deaths reported in Cohort # 2.

### **7.1.2 Other Serious Adverse Events**

#### **Cohort # 1**

Four subjects reported 8 serious adverse events, two of which occurred after the cutoff date for this submission:

- Subject 7601-107 (described above) had 5 serious adverse events: 3 events of obstructive bronchitis, one event of hepatomegaly, and one event of cardio-respiratory failure causing death.
- Subject 8802-112 has a serious adverse event of hypoglycemia. The subject, an 8.5 year-old was noted to have at the Month 1 visit a morning capillary glucose of 20 mg/dl with no associated symptoms. Hypoglycemia was confirmed in the laboratory (23 mg/dl) and the patient was briefly hospitalized. The patient had, reportedly, multiple low capillary glucose measurements previously (20/67 measurements were < 50 mg/dl) and had been missing meals and snacks. The patient received dietary counseling and had the study drug dose reduced at 0.5 mg/kg/day for one month with subsequent normalization of capillary blood glucose. When the study drug dose was increased back to 1 mg/kg/day no further

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failure and subsequent cardiac failure. Death occurred 36 days following discontinuation of study drug. The post-mortem pathology report revealed endocardial fibroelastosis, moderate mitral valve stenosis and moderate myocardial hypertrophy (with cardiac size in the upper normal range). The imminent cause of death was “purulent bronchitis and bronchopneumonia with additional signs of interstitial pneumonia, which tested positive for RSV.” The subject’s liver was considered slightly enlarged at autopsy. The sponsor states that “the severe RSV pneumonia and endocardial fibroelastosis were likely associated with the underlying mitral valve stenosis.”

hypoglycemic episodes were reported. This serious event was reported as related to study drug.

- Subject 7501-105 had a serious adverse event of adenoid hypertrophy requiring hospitalization. This 13.5-year old male received rhIGF-I/rhIGFBP-3 at 1 mg/kg for one year prior to the event. At Month 9 he had “impaired nasal breathing and ear pain.” The subject discontinued study medication after 1 year, reportedly, because the site had not obtained ethics committee approval for the 12-month study extension. The subject underwent removal of the adenoids one month after study discontinuation.
- Subject 7502-106, a 12-year old male experienced an episode of increased intracranial pressure and severe papilledema requiring hospitalization; the event was considered possibly related to study medication.<sup>72</sup>

## Cohort # 2

Two serious adverse events were reported in Cohort #2; both were considered not to be related to study treatment by the investigator:

- Subject 7701-201, a female, aged 3 years and 10 months had a gastrostomy tube placed for improvement of her nutritional status (this patient had multiple medical problems, which included severe growth failure, poor feeding, incoordinate swallow, chronic gastritis, developmental delay, hypotonia, and hypoglycemia).
- Subject 9101-210, a female aged 6 years and 7 months had an episode of hypoglycemia resulting in hospitalization after approximately 4 months of treatment.<sup>73</sup>

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<sup>72</sup> The subject, who also had a ventriculo-peritoneal shunt in place since age 1 yr. for hydrocephalus, had been treated with rhIGF-I/rhIGFBP-3 at 1.0 mg/kg daily for 12 months. He temporarily discontinued study medication for 3 months because the site had not obtained ethics committee approval for the 12-month study extension, and then re-started treatment at the same dose. Three months later he presented with left body pain sensation for 3 weeks, 2 episodes of vomiting, papilledema, reduced vision, increased intracranial pressure on MRI and in the shunt reservoir. The subject underwent an operative revision of the shunt with improvement of symptoms after surgery.

<sup>73</sup> The night before the event, she received study drug (dose: 2.0 mg/kg) without eating an evening meal and the next morning she was found unresponsive (blood glucose level of 18 mg/dL). She was taken to the emergency room and she was discharged the next day after receiving i.v. glucose. The investigator deemed this serious adverse event

On August 15, 2005 the applicant submitted limited safety information obtained with the to-be-marketed drug product manufactured at the Boulder (Colorado) site. It included data from 4 subjects from Cohort # 2 who switched from the “Avecia” drug product to the “Boulder” drug product for 3 weeks. In this dataset two serious adverse events were reported: hospitalization for weight loss and management of gastrostomy tube feedings (“not related”) and tonsillar/adenoid hypertrophy leading to adeno-tonsillectomy (“possibly related”).<sup>74</sup>

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### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

##### **Cohort # 1**

Subject 7601-107 (see death/SAE section) is described as “the only subject with early withdrawal from the study due to an adverse event [hepatomegaly].”<sup>75</sup>

##### **Cohort # 2**

The applicant reports that one patient was terminated from the clinical trial due non-compliance to treatment in Cohort #2 (Subject 8301-211).

#### 7.1.3.2 Adverse events associated with dropouts

See Section 7.1.3.1.

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“not to be related to the study medication” on the basis of the fact that the patient had previous AEs of hypoglycemia and that she did not ingest an evening meal or a midnight snack (“protocol violation”).

<sup>74</sup> 15 SAE were reported in the non-GHIS program; of these, only one was reported as possibly related to the study treatment: an elderly female in a hip fracture study had a laboratory report each of increase in serum alkaline phosphatase and gamma-glutamyl transferase respectively. Other SAEs in the same study were refracture of hip, possible new fracture, pneumonia, transient ischemic attack, and compressed ulnar nerve (placebo patient). In the severe burns study SAEs reported were septicemia, pulmonary edema, and overdose with no sequelae. In a type 2 diabetes trial two subjects reported angina and cellulitis. In the severe insulin resistance program one patient developed anemia due to blood sampling and another one had hypoglycemia and loss of consciousness.

<sup>75</sup> One patient had an incidental finding of multicystic ovaries for which mecasermin therapy was temporarily interrupted.

### 7.1.3.3 Other significant adverse events

Other significant adverse events noted in the rhIGF-I/rhIGFBP-3 dataset are ovarian cysts (one patient in Cohort # 1 and one in Cohort # 2)<sup>76</sup> and liver enzyme elevation (two patients had temporarily interrupted the treatment due to ALT elevation).

### 7.1.4 Other Search Strategies

The small size of the safety dataset, the absence of a control group, and the limited exposure were not conducive to additional safety analyses.

### 7.1.5 Common Adverse Events

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

Patients enrolled in the clinical trial were evaluated with complete physical examinations (including fundoscopy and vital signs) at baseline, Day 4, Month 1, and every 3 months post-baseline. The injection sites were assessed at every visit (any abnormality was to be documented as an AE). Adverse events (as well as concomitant medication, drug accountability, subject compliance, and subject diaries) were assessed at all visits.

Ongoing adverse events at the final study visit were to be followed until the event was resolved or remained stable; serious adverse events that occurred within 30 days

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<sup>76</sup> In Cohort # 1, subject 7401-119, a 3.1-year old female, was found on abdominal ultrasound to have cystic ovaries. Study medication was discontinued for 4 months (Month 5 through Month 9) and was resumed after the “almost complete” disappearance of the ovarian cysts. This finding resulted in a protocol amendment change which specified the addition of pelvic ultrasound of the uterus and ovaries in female subjects. This patient was prepubertal at baseline and had a normal size uterus (ovaries were not visualized). “A pelvic ultrasound performed at approximately Month 4 showed ovarian cysts bilaterally, approximately 3-4 cysts/ovary, resulting in ovarian dimensions of approximately 15x16x17 mm bilaterally. A third ultrasound, obtained one month later showed similar findings with respect to the previous ultrasound with the ovaries perhaps 1-2 mm larger. At Month 6 (off treatment for 1 month) pelvic ultrasound showed decreased ovarian size. No evidence of hyperandrogenism, sexual precocity, galactorrhea, or vaginal mucosal changes has been reported; a rise in serum estrogen levels was present (testosterone was undetectable). In Cohort # 2, Subject, 9302-204 had ovarian cysts noted on the Month 6 ultrasound (the ovaries were not described on the baseline ultrasound). The left ovary was not visualized but the right ovary had multiple cysts 3-4 mm in size. Estradiol ( 7.38 pg/mL) and testosterone (0.021 ng/mL) were measured within normal range. The adverse event was considered mild and possibly related (this subject also developed hypothyroidism at Month 3 and was treated with thyroxine).

following the final study visit were to be reported to the applicant by individual sites. The following information was to be recorded for each adverse event: the AE term, start and stop dates, severity (mild, moderate, or severe), seriousness (serious or non-serious), action taken regarding study medication (none, study medication dose reduced, study medication interrupted, or study medication stopped), action taken regarding AE (specific treatment instituted, subject hospitalized, etc.), outcome (resolved, ongoing, death, or lost to follow-up), and causality to study medication (not related, possibly related, related).

#### 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 in Appendix. 16.2.71. The two types of terms were concordant.

#### 7.1.5.3 Incidence of common adverse events

##### **Cohort # 1**

Each study subject experienced at least one adverse event (AE). A total of 148 AEs were reported by the 19 subjects during the trial. Most AEs were, reportedly, mild in intensity. Adverse events that occurred in two or more patients ( $\geq 11\%$ ) in Cohort # 1 are presented in Table 6 (derived from applicant’s Table 13 of Clinical Study Report Cohort #1, Report # 2). The table also provides information on whether the events were deemed related to study drug by the investigator. Injection site conditions were the most common treatment-emergent adverse event (TEAE); the preferred terms related to injection site TEAEs were erythema (13 subjects), hypertrophy (11 subjects; reported as lipohypertrophy), induration (5 subjects), pain (3 subjects), pigmentary changes (6 subjects), pruritus (2 subjects), “reaction” (10 subjects), and urticaria (1 subject).<sup>77</sup> Eight adverse events of hypoglycemia were reported in 7 subjects (37%); of these, 6 events were reported at Month 1, one event each at Months 2 and 3, and none thereafter; only one event each

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<sup>77</sup> All of these adverse events were considered mild and moderate in intensity.

was rated moderate and severe, all others were reported as mild.<sup>78</sup> Other frequent TEAEs were headache (all episodes were mild or moderate) and upper respiratory tract infection. All other TEAEs occurred in two patients (or less).<sup>79</sup> The adverse events that were considered treatment-related in all cases were those related to the injection site, hypoglycemia, bone pain, muscular atrophy, pain in extremity, and tonsillar hypertrophy. Headache was another adverse event which, in a large proportion of patients, was considered treatment-related by the investigators. Only three TEAEs were rated severe: hypoglycemia, tooth disorder, and infected eczema; of these, only the adverse events of hypoglycemia and tooth disorder were considered treatment related by the investigator. The absence of a control group limits the ability to draw further conclusions.

**Table 6: Incidence of Adverse Events Occurring in  $\geq 2$  Patients ( $\geq 11\%$ ) in Cohort # 1**

Adverse event	Number and (%) of patients with event N=19	Number and (%) of patients with event considered "related" N=19
Inj site erythema	13 (68%)	13 (68%)
Inj site hypertrophy	11 (58%)	11 (58%)
Inj site reaction	10 (53%)	10 (53%)
Hypoglycemia	7 (37%)	7 (37%)
Headache	7 (37%)	5 (26%)
Inj site pigmentation changes	6 (32%)	6 (32%)
Inj site induration	5 (26%)	5 (26%)
Upper resp. tract infection	5 (26%)	0 (0%)
Inj site pain	3 (16%)	3 (16%)
Iron deficiency anemia	2 (11%)	1 (5%)
Otitis media	2 (11%)	1 (5%)
Diarrhea	2 (11%)	0 (0%)
Inj site pruritis	2 (11%)	2 (11%)

<sup>78</sup> Subject 7201-117 had a hypoglycemic event that was symptomatic and that required treatment with an oral glucose gel. The event occurred on the morning of Day 10 of study and was rated moderate in severity. Another subject (8802-112) was hospitalized for the treatment of asymptomatic hypoglycemia (see description in SAE section). The average number of hypoglycemia events per month per subject was 0.06.

<sup>79</sup> Several TEAEs are of particular interest given the published literature with rhIGF-I and/or rhGH. Hindered nasal breathing (coded to preferred term nasal disorder) was reported in 2 subjects, including a subject who subsequently underwent adenoidectomy. Tonsillar hypertrophy was reported in 2 subjects (including one of the subjects with hindered nasal breathing). Six subjects reported ear disorders (otitis or unilateral deafness). Two subjects were reported with extremity and bone pain and one subject with arthralgia.

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Lethargy	2 (11%)	1 (5%)
Pyrexia	2 (11%)	1 (5%)
Rhinitis	2 (11%)	0 (0%)
Viral infection	2 (11%)	1 (5%)
Bone pain	2 (11%)	2 (11%)
Muscular atrophy	2 (11%)	2 (11%)
Pain in extremity	2 (11%)	2 (11%)
Dizziness	2 (11%)	1 (5%)
Nasal disorder	2 (11%)	1 (5%)
Tonsillar hypertrophy	2 (11%)	2 (11%)

Source: Table # 13 of Clinical Study Report Cohort #1, Report # 2.

## Cohort # 2

Each of the ten subjects in Cohort #2 experienced at least one AE on study drug. There was a total of 52 adverse events. All but one adverse event were reported as mild to moderate. Adverse events that occurred in two or more patients ( $\geq 20\%$ ) are presented in Table 7 (derived from applicant's Table 14 from the Clinical Study Report Cohort #2, Report # 2). The table also provides information on whether the events were deemed related to the study drug by the investigator. The most common adverse events were injection site conditions, which included the following preferred terms: "reaction," erythema, hypertrophy, and pigmentation changes. Five (50 %) subjects reported upper respiratory tract infections and four (40%) subjects reported hyperglycemia during the first month of the study.<sup>80</sup> Three (30%) subjects reported 8 events of hypoglycemia (all but one were considered mild and all were deemed possibly related to study treatment).<sup>81</sup> Two subjects had elevated transaminases.<sup>82</sup> Two subjects were reported with hematuria. Two subjects were reported with tonsillar hypertrophy and one subject each with splenomegaly and lymphadenopathy. One subject was diagnosed with hypothyroidism and was treated with thyroxine; the same subject was later reported to have ovarian cysts. One subject

<sup>80</sup> All episodes of hyperglycemia were considered mild and they were deemed possibly related to study drug in 3 cases (which were reported for Day 1 prior to dosing). The fourth case was reported at Month 1 and was not considered related to treatment.

<sup>81</sup> Subject 9101-210 reported 5 episodes of asymptomatic hypoglycemia and one event of symptomatic hypoglycemia (see Section on SAEs). Subject 9302-204 reported symptomatic hypoglycemia in the morning on one occasion in the first month. The third subject (9301-203) reported one episode of hypoglycemia at Month 5. Overall, only two subjects had symptomatic hypoglycemia

<sup>82</sup> Subject 8301-211 was found to have elevated transaminases at the Month 3 visit; treatment was interrupted for six weeks. Subsequently transaminases returned to normal and treatment was restarted. For another subject (8806-208) the event of transaminase elevation was reported as hepatotoxicity, r/o viral hepatitis (hepatitis antibody tests in this subject were all negative and transaminases returned to normal after a 10-day interruption and medication was restarted).

each was reported with pulmonary hypertension, anemia, and gastrostomy tube insertion. Adverse events that were considered treatment-related in all cases were those related to the injection site, hypoglycemia, increased transaminases, hematuria, and tonsillar hypertrophy.

**Table 7: Incidence of Adverse Events Occurring in  $\geq 2$  Patients ( $\geq 20\%$ ) in Cohort # 2**

Adverse event	Number and (%) of patients with event N=10	Number and (%) of patients with event considered "related" N=10
Inj site reaction	6 (60%)	6 (60%)
Upper resp. tract infection	5 (50%)	1 (10%)
Inj site erythema	4 (40%)	4 (40%)
Inj site hypertrophy	4 (40%)	4 (40%)
Hyperglycemia	4 (40%)	3 (30%)
Hypoglycemia	3 (30%)	3 (30%)
Inj site pigmentation changes	2 (20%)	2 (20%)
Transaminases Increased	2 (20%)	2 (20%)
Hematuria	2 (20%)	2 (20%)
Tonsillar hypertrophy	2 (20%)	2 (20%)

Source: Table # 14 from the Clinical Study Report Cohort #2, Report # 2.

Table 8 depicts the number and percentage of patients with TEAEs across both Cohort # 1 and Cohort # 2.<sup>83</sup> Adverse events are listed in decreasing order of frequency (included are only adverse events which occurred in  $\geq 6.9\%$  or  $\geq 2$  patients). Table 8 re-formats applicant's Table 15 from Clinical Study Report Cohort # 2, Report # 2. The most common adverse events were those related to the injection site followed by URI, hypoglycemia, headache, hyperglycemia, and tonsillar hypertrophy. Adverse events which occurred in 2 patients each were iron deficiency anemia, lymphadenopathy, otitis media, diarrhea, injection site pruritis, lethargy, pyrexia, rhinitis, viral infection, injury, transaminases increased, bone pain, muscular atrophy, pain in extremity, dizziness, hematuria, ovarian cyst, and nasal disorder.

**Table 8: Incidence of Adverse Events Occurring in  $\geq 2$  Patients ( $\geq 10.3\%$ ) Across Cohorts #1 and # 2\***

Adverse event (preferred term)	Number and % of patients with adverse event N= 29
Inj site erythema	17 (58.6%)
Inj site reaction	16 (55.2%)
Inj site hypertrophy	15 (51.7%)
Upper respiratory tract infection	10 (34.5%)

<sup>83</sup> Duration of treatment: 12 months for Cohort # 1 and 6 months for Cohort # 2.

Hypoglycemia	10 (34.5%)
Inj site pigmentation changes	8 (27.6%)
Headache	7 (24.1%)
Inj site induration	5 (17.2%)
Hyperglycemia	4 (13.8%)
Tonsillar hypertrophy	4 (13.8%)
Inj site pain	3 (10.3%)
Iron deficiency anemia	2 (6.9%)
Lymphadenopathy	2 (6.9%)
Otitis media	2 (6.9%)
Diarrhea	2 (6.9%)
Inj site pruritis	2 (6.9%)
Lethargy	2 (6.9%)
Pyrexia	2 (6.9%)
Rhinitis	2 (6.9%)
Viral infection	2 (6.9%)
Injury	2 (6.9%)
Transaminases Increased	2 (6.9%)
Bone pain	2 (6.9%)
Muscular atrophy	2 (6.9%)
Pain in extremity	2 (6.9%)
Dizziness	2 (6.9%)
Hematuria	2 (6.9%)
Ovarian cyst	2 (6.9%)
Nasal disorder	2 (6.9%)

Source: Table 15 from Clinical Study Report Cohort # 2, Report # 2.

\* Mean duration of treatment equals 9.3±3.6 months (range 3.2 - 12.7)

On August 15, 2005 the applicant submitted limited safety information obtained with the to-be-marketed drug product manufactured at the Boulder (Colorado) site. This report includes safety data on 4 subjects from Cohort # 2 who switched from the “Avecia” drug product to the “Boulder” drug product. The duration of exposure is very short (3 weeks). Compliance with the study drug was reported to be 100%. All patients received 2 mg/kg of rhIGF-I/rhIGFBP-3 daily. Five adverse events were reported in 2 of the 4 subjects. They were dry skin (“not related”), microscopic hematuria, iron deficiency anemia, injection site lipohypertrophy, and worsening of congenital hip dislocation (all four were considered “possibly related”). A subsequent submission included one month of safety data obtained from 4 additional (treatment-naïve) patients treated for one month with the “Boulder” drug product. Six TEAEs were reported in these 4 patients; all TEAEs were injection site reactions rated as mild in intensity.

#### 7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.3.

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

Refer to Section 7.1.5.3.

### 7.1.5.6 Additional analyses and explorations

At the request of the division the applicant conducted several investigations that evaluated the potential risk for organomegaly, hearing loss and retinopathy.<sup>84</sup> They were conducted in subsets of patients enrolled in the clinical trial and included echocardiograms, ECGs, abdominal ultrasounds, audiograms and fundoscopic exams, all to be performed at baseline, Month 6 and at Month 12. ECG results are summarized in Section 7.1.9.

#### Cohort # 1

Fourteen of 19 patients had echocardiograms performed at baseline. There were only two patients with abnormal echocardiographic findings at baseline; both had normal echocardiograms at Month 12 (patient 7901-104 had mild tricuspid incompetence/thickened interventricular septum<sup>85</sup> and patient 8802-112 had a minimal gradient on pulmonary artery (17 mm Hg).<sup>86</sup> At Month 6 and Month 12, eleven patients and 13 patients respectively, had echocardiographic evaluations; most of them were normal. Two patients with normal echocardiograms at baseline had abnormal findings on trial (patient 7301-110 had mild tricuspid regurgitation at Month 12 and patient 7601-107 had moderate mitral valve stenosis at Month 6; only the latter was considered clinically significant (see SAE for subject 7601-107 at Month 6 in Section 7.1.1). Table 9 summarizes the echocardiographic information presented for Cohort # 1.

**Table 9: Summary of Echocardiographic findings – Cohort # 1 (safety Population)**

Visit	Test Result	N (%)
Baseline	Normal	12 (85.7 %)
	Abnormal but clinically insignificant	2 (14.3%)
	Abnormal and clinically significant	0 (0%)
Month 6	Normal	9 (81.8 %)
	Abnormal but clinically insignificant	1 (9.1 %)
	Abnormal and clinically significant	1 (9.1 %)
Month 12	Normal	12 (92.3 %)
	Abnormal but clinically insignificant	1 (7.7 %)
	Abnormal and clinically significant	0 (0 %)

Source: Appendix 14.3.5.6 (modified in submission 0027, August 23, 2005)

<sup>84</sup> These evaluations were requested because published data with rhIGF-I treatment in patients with GHIS indicate a potential risk for organomegaly and hearing loss.

<sup>85</sup> On follow-up the exam was within normal limits with only trace tricuspid incompetence at Month 6 and entirely normal at Month 12.

<sup>86</sup> Follow-up at Month 6 showed similar findings with a systolic gradient on the pulmonary artery of 25 mm and a 16 mm Hg gradient in the descending aorta; at Month 12, however, the echocardiogram results were completely normalized.

Abnormal audiograms were reported in 6/15 subjects at baseline; only one of these was considered clinically significant.<sup>87</sup> At Month 6, 5/12 subjects had abnormal audiograms, with one considered clinically significant.<sup>88</sup> At Month 12, 7/14 subjects had abnormal audiograms with clinically significant findings in two additional subjects.<sup>89</sup>

The applicant reports that “[abdominal] ultrasound results were considered normal in most subjects at Baseline, Month 6 and Month 12.” Baseline abnormalities included small kidneys, slightly enlarged spleen, slightly coarse parenchyma, and unilateral kidney dysplasia in one subject each. Evaluations performed at Month 6 and 12 indicated “growth of the spleen and variable changes in liver and kidney size in most subjects.” One subject (7601-107) had hepatomegaly (see SAE described in Section 7.1.1 for details). Another subject (8804-114) had bilateral medullary nephrocalcinosis (not reported by the investigator as an adverse event). A 3.1-year old female (subject 7401-119) was found to have cystic ovaries. The data presented in the submission is purely descriptive in some patients (e.g. “normal renal exam”) while for other patients numerical values (e.g. kidney and spleen length) are provided. At the request of this reviewer the applicant has provided graphic displays including normative standards for those patients with quantitative data. They indicate that renal and spleen growth exhibits a catch up growth phenomenon just like linear growth. The vast majority of values are within normal values for chronological age with only occasional measurements close to the upper limit of normal.

All patients had fundoscopic examinations; they were normal (i.e. no evidence of retinopathy) at all visits.<sup>90</sup>

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<sup>87</sup> Subject, 7501-105 had an abnormal audiogram at baseline. At Month 6 findings were unchanged. At Month 12 they were described as “due to adenoid hypertrophy.” The subject later had surgical removal of adenoids (see SAE in Section 7.12).

<sup>88</sup> Subject, 8202-102 had unilateral, conductive hearing loss associated with recurrent secretory otitis media and flat tympanum reported at Months 6 and 12; there was no baseline audiogram in this patient.

<sup>89</sup> Subjects 8701-108 and 8702-109 had hearing impairment associated with middle ear effusion and eardrum defect, respectively at Month 12. Both subjects lacked baseline audiograms. Both had audiograms performed at Month 3 which showed bilateral middle ear effusion associated with hyperplastic tonsils/adenoids and unilateral eardrum defect and retraction, respectively.

<sup>90</sup> A few patients did not have on occasions fundoscopic assessments; in all cases subsequent assessments were normal.

**Cohort # 2**

All 10 had echocardiograms performed at baseline; only two patients had abnormal findings (described as “not clinically significant”). They were mitral valve insufficiency and small PDA. There were 8 follow-up echocardiograms at Month 6; among these there was only one new abnormal finding in a patient who had a normal exam at baseline: “mild pulmonary hypertension, first degree triscupis AFT insufficiency.”<sup>91</sup> Table 10 summarizes the echocardiographic information presented for Cohort # 2.

**Table 10: Summary of Echocardiographic Findings – Cohort # 2 (safety Population)**

Visit	Test Result	N (%)
Baseline	Normal	8 (80 %)
	Abnormal but clinically insignificant	2 (20%)
	Abnormal and clinically significant	0 (0 %)
Month 6	Normal	6 (75 %)
	Abnormal but clinically insignificant	1 (12.5 %)
	Abnormal and clinically significant	1 (12.5 %)

Source: Appendix 14.3.5.6 (modified in submission 0027, August 23, 2005)

The applicant reports that 2/9 patients had abnormal audiograms at baseline, 1/7 had abnormal audiograms at Month 6 and that all the abnormal audiograms “were characterized as not clinically significant.”

Abdominal ultrasounds (and later pelvic ultrasounds) results are described as follows: “in subjects with serial measurements at baseline and Month 6, spleen size enlarged, liver size increased in some and decreased in others, and kidney size increased.” Adverse events related to organomegaly were reported in two subjects.<sup>92</sup>

<sup>91</sup> Subject 9301-203 had mild pulmonary hypertension and first degree tricuspid insufficiency. This finding was reported as a mild adverse event possibly related to study drug. The subject has temporarily discontinued study drug (the applicant states that “detailed data regarding this event was not received by the cut-off date for this study report”).

<sup>92</sup> Subject, 9302-204 had ovarian cysts noted on the Month 6 ultrasound (the ovaries were not described on the baseline ultrasound). Subject 9301-203 had an enlarged spleen was enlarged beyond the normal range for age (the spleen was assessed as normal at baseline but baseline measurements of the spleen

All patients had fundoscopic examinations which were normal at all visits.

### 7.1.6 Less Common Adverse Events

#### **Cohort # 1**

Adverse events that occurred in only one patient (5 %) and were considered by the investigator to be drug-related were lymphadenopathy, ear pain, tooth disorder, crying, hunger, injection site urticaria, "therapeutic response decr.", hepatomegaly, hepatic steatosis, arthralgia, ovarian cyst, milia, and pruritus.

Adverse events that occurred in only one patient (5 %) and were not considered by the investigator to be drug-related were unilateral deafness, impaired-hearing, middle ear effusion, perforation of tympanic membrane, upper abdominal pain, constipation, nausea, vomiting, lower respiratory tract infection, lymph gland infection, accident, injury, decreased appetite, bronchitis, cough, dyspnea, epistaxis, nasopharyngitis, rhinorrhea, and infected eczema.

#### **Cohort # 2**

Adverse events that occurred in only one patient (10 %) and were considered by the investigator to be drug-related were iron deficiency anemia, splenomegaly, hypothyroidism, ovarian cyst, and pulmonary hypertension.

Adverse events that occurred in only one patient (10 %) and were not considered by the investigator to be drug-related were lymphadenopathy, fever, injury, and gastrostomy tube insertion.

### 7.1.7 Laboratory Findings

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

Standard chemistry, hematology, and urinalysis testing was performed at baseline, Day 4, Month 1, and every 3 months post-baseline during Year 1 (and is to be performed every 6 months during Year 2). Capillary blood glucose was measured twice daily for 3 days pre-baseline, 30 days post-baseline, and in the event of a hypoglycemic episode thereafter. Serum

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were not available for comparison). The adverse event of splenomegaly was described as mild and possibly related to study drug..

IGF-I, IGF-II, IGFBP-3, and ALS levels, were assessed at baseline, Month 1, and every 3 months post-baseline in Year 1 (and are to be assessed every 6 months thereafter and in the event of increase in dose). Antibodies to IGF-I, IGFBP-3 and IGF-I/IGFBP-3 were assessed at baseline, Month 1 (second cohort only), and every 3 months post-baseline in Year 1 (and are to be assessed every 6 months thereafter and in the event of increase in dose). Pharmacokinetics of IGF-I and IGFBP-3 during treatment with rhIGF-I/rhIGFBP-3 were performed on a subset of subjects (by determining Cmax, Cmaxtot, Tmax, and AUC(0-24) from 24-hour blood sampling at baseline, Month 3, and Month 6).

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

Not applicable (there was no control group).

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

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

### Hematology

#### Cohort # 1

The applicant does not report any clinically meaningful changes in mean values for standard hematology analytes. Table 11 summarizes the mean values and the change from baseline to Month 12 for hemoglobin, platelet counts, white cell counts, and eosinophil counts.

**Table 11: Selected Hematology Analytes for Cohort # 1 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Month 12	Change from baseline to Month 12
<b>Hemoglobin</b> (mmol/L)					
N	19	18	17	15	15
Mean (SD)	7.3 (0.5)	7.2 (0.7)	7.3 (0.8)	7.67 (0.6)	0.37 (0.4)
Median	7.4	7.1	7.2	7.5	0.37
Range	6.1-8.1	5.7-8.3	5.7-9	6.5-8.8	-0.43-1.0
<b>Platelets</b> (x10 <sup>9</sup> /L)					
N	19	18	17	15	15
Mean (SD)	362.2 (76.7)	328.8 (114)	296.8 (85.7)	292.8 (80.7)	-81.33 (72.6)
Median	358	299.5	325	279	-92
Range	238-598	154-588	49-415	173-436	-235-29
<b>WBC</b> (x10 <sup>9</sup> /L)					
N	19	18	17	15	15
Mean (SD)	8.6 (1.4)	7.8 (1.9)	8.2 (1.9)	8.6 (2.2)	-0.04 (1.3)

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Median	8.8	7.6	8.2	8.7	0.46
Range	5.9-11.9	4.4-12.3	4.6-11.2	5-12.9	-2.5-1.8
<b>Eosinophils</b> (x10 <sup>9</sup> /L)					
N	19	17	17	14	14
Mean (SD)	0.4 (0.4)	0.3 (0.2)	0.3 (0.2)	0.5 (0.5)	0.06 (0.5)
Median	0.3	0.2	0.3	0.3	0.05
Range	0.1-2	0.1-1.1	0.1-3.9	0.1-2.1	-1.0-1.1

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

## Cohort # 2

No meaningful changes in mean values for standard hematology analytes were recorded in Cohort # 2. Table 12 summarizes the mean values and the change from baseline to Month 6 for hemoglobin, platelet counts, white cell counts, and eosinophil counts.

**Table 12: Selected Hematology Analytes for Cohort # 2 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Change from baseline to Month 6
<b>Hemoglobin</b> (mmol/L)				
N	8	9	9	7
Mean (SD)	6.8 (0.6)	6.6 (0.8)	6.9 (1.1)	0.4 (1.2)
Median	6.8	6.3	7.1	0.5
Range	5.7-7.7	5.2-8.0	5.2-8.9	-0.8-2.7
<b>Platelets</b> (x10 <sup>9</sup> /L)				
N	8	9	9	7
Mean (SD)	360.2 (104.7)	373.1 (98.4)	335.8 (72.5)	-28.5 (72.1)
Median	357	350	314	-40
Range	199-504	244-561	245-427	-100-115.5
<b>WBC</b> (x10 <sup>9</sup> /L)				
N	8	9	9	7
Mean (SD)	11.1 (2.4)	10.9 (2.40)	9.0 (1.8)	-2.0 (3.0)
Median	10.8	10.6	8.4	-2.2
Range	8.7-16	6.8-14.9	7.-12	-5.8- -1.5
<b>Eosinophils</b> (x10 <sup>9</sup> /L)				
N	8	9	9	7
Mean (SD)	0.2 (0.1)	0.22 (0.1)	0.24 (0.1)	0.09 (0.1)
Median	0.2	0.2	0.2	0.1
Range	0.0-0.30	0.00-0.50	0.1-0.6	-0.1-0.3

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 2, Report # 2).

## Chemistry, capillary blood glucose

## Electrolytes

### Cohort # 1

There were no clinically relevant changes from baseline to Month 12 in the mean values for sodium, potassium, chloride, phosphate, calcium and magnesium (Table 13).

**Table 13: Electrolytes - Cohort # 1 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Month 12	Change from baseline to Month 12
<b>Sodium (mmol/L)</b>					
N	19	15	17	15	15
Mean (SD)	137.7 (2.3)	138.2 (1.7)	139.6 (1.9)	138.4 (2.6)	0.73 (4.3)
Median	137.10	138	140	139	1.00
Range	135-145	136-142	136-143	132-142	-10-6.0
<b>Potassium (mmol/L)</b>					
N	19	15	16	15	15
Mean (SD)	4.1 (0.4)	4.1 (0.3)	3.9 (0.4)	4.2 (0.3)	0.09 (0.4)
Median	4.1	4.2	3.9	4.2	0.1
Range	3.3-4.8	3.5-4.7	3.2-4.9	3.5-4.8	-0.60-0.80
<b>Chloride (mmol/L)</b>					
N	18	11	14	11	10
Mean (SD)	105.8 (2.6)	104.2 (5.5)	107.2 (2.7)	107.6 (3.4)	0.7 (4.1)
Median	106	105	108.5	107	1.5
Range	101-110	96-112	102-110	100-113	-9.0 - 7.0
<b>Phosphate (mmol/L)</b>					
N	18	14	15	13	12
Mean (SD)	1.4 (0.2)	1.6 (0.3)	1.6(0.2)	1.5 (0.2)	0.18 (0.2)
Median	1.42	1.65	1.71	1.6	0.2
Range	1.0-1.7	1.2-2.1	1.2-2.0	0.8-1.9	-0.2 - 0.5
<b>Calcium (mmol/L)</b>					
N	18	17	17	14	14
Mean (SD)	2.4 (0.1)	2.4 (0.1)	2.39 (0.1)	2.4 (0.1)	0.04 (0.1)
Median	2.4	2.4	2.3	2.4	0.05
Range	2.2-2.7	2.3-2.6	1.9-2.6	2.0-2.5	-0.29-0.23
<b>Magnesium (mmol/L)</b>					
N	15	10	13	10	10
Mean (SD)	0.8 (0.07)	0.8 (0.08)	0.8 (0.04)	0.8 (0.06)	-0.02 (0.03)
Median	0.8	0.82	0.8	0.8	-0.06
Range	0.7-0.9	0.6-0.9	0.7-0.8	0.7-0.9	-0.1 -0.16

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

**Cohort # 2**

Similar to observations made in Cohort # 1 there were no clinically meaningful changes in serum electrolytes for up to 6 months of treatment (Table 14). The applicant states that

Mean serum calcium and magnesium levels did not change with treatment. Mean serum phosphate levels increased during treatment, as was seen in Cohort #1. Mean uric acid levels decreased during treatment, with most subjects having low levels during treatment.

**Table 14: Electrolytes - Cohort # 2 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Change from baseline to Month 6
<b>Sodium (mmol/L)</b>				
N	10	10	9	9
Mean (SD)	136.9 (2.6)	138 (3.3)	141.7 (3.0)	4.8 (5.2)
Median	137.5	139	142	3.0
Range	132-140	133-143	138-145	-2-13
<b>Potassium (mmol/L)</b>				
N	10	10	9	9
Mean (SD)	4.1 (0.2)	4.1 (0.1)	4.0 (0.3)	0.04 (0.3)
Median	3.9	4.1	4.05	0.1
Range	3.7-4.3	3.8-4.4	3.7-3.6	-0.59-0.39
<b>Chloride (mmol/L)</b>				
N	9	9	8	8
Mean (SD)	102 (3.1)	103 (3.8)	107.7 (3.7)	5.6 (3.8)
Median	103	102	108.5	5.0
Range	95-105	98-109	101-114	-1.0-10.0
<b>Phosphate (mmol/L)</b>				
N	8	10	9	8
Mean (SD)	1.5 (0.7)	1.8 (0.2)	1.7 (0.1)	0.1 (0.1)
Median	1.4	1.8	1.7	0.1
Range	1.2-1.9	1.1-2.1	1.4-2	-0.06
<b>Calcium (mmol/L)</b>				
N	10	10	9	9

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Mean (SD)	2.4 (0.08)	2.5 (0.09)	2.4 (0.1)	-0.05 (0.1)
Median	2.4	2.5	2.4	-0.02
Range	2.3-2.6	2.4-2.6	2.1-2.5	-0.36-0.1
<b>Magnesium</b> (mmol/L)				
N	8	5	8	7
Mean (SD)	0.8 (0.06)	0.8 (0.03)	0.8 (0.04)	0.0 (-.06)
Median	0.8	0.8	0.8	0.04
Range	0.7-0.9	0.7-0.8	0.8-0.9	-0.09-0.08

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

## BUN, Creatinine and Uric Acid

### Cohort # 1

Descriptive statistics for renal function tests (BUN, creatinine, creatinine clearance) and uric acid) are presented in Table 15 which summarizes information presented in Appendix 14.3 4.1 of the Clinical Study Report (Cohort # 1, Report # 2). There were no clinically relevant changes in mean values from baseline to Month 12. The applicant states that “Decreases in mean BUN levels were consistent with the anabolic effects of treatment. Mean calculated creatinine clearance increased during treatment.”

**Table 15: BUN, Uric Acid and Creatinine for Cohort # 1 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Month 12	Change from baseline to Month 12
<b>BUN</b> (mmol/L)					
N	19	12	17	15	15
Mean (SD)	6.1 (1.6)	4.18 (1.1)	4.1 (1.2)	5.1 (2.8)	-0.84 (2.6)
Median	5.7	3.7	3.9	4.28	-0.7
Range	3.7-8.9	3.1-6.7	2.3-6.4	2.4-12.14	-4.6 -5.0
<b>Uric acid</b> ( $\mu$ mol/L)					
N	15	10	13	14	12
Mean (SD)	204.2 (43.9)	139.4 (68.3)	159.9 (44.1)	171.4 (84.9)	-62.9 (50.3)
Median	198.6	142.3	170	160.5	-70.5
Range	118.6-273	55.3-280	72.5-220	60-339	-137 - 20
<b>Creatinine</b> ( $\mu$ mol/L)					
N	19	13	17	15	15
Mean (SD)	37 (12.7)	26.2 (14.4)	26.8 (11.9)	33.7 (10.4)	-3.39 (9.2)
Median	36.24	20.3	26	35.3	-3.5
Range	17-64)	11-52	9.7-51	17.6-50	-26 - 8.8
<b>Creatinine clearance*</b> (ml/min/1.73 m <sup>2</sup> )					

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N	18	12	17	15	14
Mean (SD)	138 (43.6)	198.2 (86.9)	212.9 (99.9)	162.9 (49.3)	27.7 (48)
Median	134	196.7	197.7	166.3	24.8
Range	87.8-214.5	93.4-360.7	97.2-448.5	90.1-242.3	-41.8-146.1

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

\*Estimated using the Schwartz equation.

## Cohort # 2

Descriptive statistics for renal function tests (BUN, creatinine, creatinine clearance) and uric acid) for Cohort # 2 are presented in Table 16 which summarizes information presented in Appendix 14.3 4.1 of the Clinical Study Report (Cohort # 2, Report # 2). There were no clinically relevant changes in mean values from baseline to Month 6. The applicant states that

“Decreases in mean BUN levels were seen, as occurred in Cohort #1, consistent with the anabolic effects of treatment.” [...]“Mean serum creatinine levels decreased during treatment, and mean calculated creatinine clearance increased, as was seen in Cohort #1 and was expected for study treatment.”

**Table 16: BUN, Uric Acid and Creatinine for Cohort # 2 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Change from baseline to Month 6
<b>BUN</b> (mmol/L)				
N	9	9	9	8
Mean (SD)	6.7 (3.2)	4.6 (3.2)	4.0 (2.3)	-2.41 (1.8)
Median	6.0	3.3	3.7	-2.2
Range	3.9-14.2	1.7-12.6	1.7-9.2	-4.6-0.7
<b>Uric acid</b> (µmol/L)				
N	9	5	8	8
Mean (SD)	176.2 (41.6)	88 (20.2)	84.7 (45.6)	-92.8 (70.3)
Median	166.5	83.8	92.1	-86.2
Range	130.8-231.9	60-113	5.9-142.7	-226 - -5.9
<b>Creatinine</b> (µmol/L)				
N	10	10	9	9
Mean (SD)	36.8 (6.6)	27.4 (5.6)	24 (6.3)	-11.9 (5.6)
Median	36.6	26.5	22.1	-12
Range	26.5-44.2	17.6-35.3	17.9-35.3	-17.6 -0.0
<b>Creatinine clearance*</b> (ml/min/1.73 m2)				

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N	10	10	9	9
Mean (SD)	119.1 (31.4)	164.3 (43.9)	192.4 (52.6)	72.8 (36.4)
Median	115.5	159.7	178.5	77.7
Range	82.9-170.8	105.8-266.2	132.3 -271.8	7.7-128

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 2, Report # 2).

\*Estimated using the Schwartz equation.

## Glucose, Total Protein, Albumin, Alkaline Phosphatase

### Cohort # 1

Descriptive statistics for serum glucose, total protein, albumin, and alkaline phosphatase are presented in Table 17. These were no clinically meaningful changes in mean values through Month 12. The applicant states that

“Mean pre-breakfast glucose values ranged from 87.1 to 88.5 mg/dL during the run-in period and between 74 and 90 mg/dL on treatment (n ranged from 12 to 18). Mean pre-dinner glucose values ranged from 100.7 to 107.9 mg/dL during the run-in period and between 93.6 and 110.9 mg/dL on treatment (n =14-18).  
 [...]Mean serum glucose levels did not decrease during treatment.”

The applicant also states that “increases in mean alkaline phosphatase levels were likely due to stimulated bone formation.”

**Table 17: Glucose, Total Protein, Albumin, and Alkaline Phosphatase for Cohort # 1 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Month 12	Change from baseline to Month 12
<b>Glucose (mmol/L)</b>					
N	17	15	14	13	11
Mean (SD)	4.2 (0.8)	5.4 (1.4)	4.7 (0.9)	4.1	0.1 (0.9)
Median	3.72	4.9	4.7	4.3	0.1
Range	3.3-6.5	3.6-8.3	3.1-6.2	2.7-5	-0.9-1.6
<b>Total protein (g/L)</b>					
N	17	11	14	14	14
Mean (SD)	72.2 (4.3)	71.5 (4.7)	71.7 (3.7)	72.9 (5.4)	0.21 (4.9)
Median	72	73	72.5	72	0.0
Range	66-80	65-77	66.7-77	64-81	-9.9-10.0
<b>Albumin (g/L)</b>					

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N	17	13	14	11	11
Mean (SD)	43.4 (3.9)	44.2 (3.5)	42.9 (1.8)	42.2 (3.4)	0.09 (2.1)
Median	43	44	42	42	1.0
Range	38-54	39-53	41-47	34-47	-4.0 -3.0
<b>Alk. Phosphatase (µkat/L)</b>					
N	19	16	17	15	15
Mean (SD)	3.7 (1.4)	4.4 (1.6)	4.6 (1.4)	3.9 (1.2)	0.2 (0.5)
Median	3.4	4.1	4.6	4.0	0.2
Range	2.23-7.2	1.8-8.0	2.7-7.5	2.4-7.0	-0.8-1.0

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

## Cohort # 2

Descriptive statistics for serum glucose, total protein, albumin, and alkaline phosphatase are presented in Table 18. These were no meaningful changes in mean values through Month 6. The applicant states that

“Mean pre-breakfast glucose values ranged from 77.0 to 87.5 mg/dL during the run-in period and between 67.5 to 86.9 mg/dL on treatment (n=4-10). Mean pre-dinner glucose values ranged from 75.8 to 90.2 mg/dL during the run-in period and between 85.4 to 107.9 mg/dL on treatment (n=5-10).” “Mean serum glucose levels were stable during the first six months of treatment.”

The applicant states also that “The increase in mean alkaline phosphatase levels were likely due to stimulated bone formation, as was seen in Cohort #1.”

**Table 18: Glucose, Total Protein, Albumin, and Alkaline Phosphatase - Cohort # 2 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Change from baseline to Month 6
<b>Glucose (mmol/L)</b>				
N	9	9	8	8
Mean (SD)	4.4 (1.1)	5.0 (0.9)	4 (0.8)	-0.44 (1.4)
Median	4.2	5	3.9	-0.33
Range	2.7-6.3	3.5-6.3	2.8-5.5	2.7 - 1.3
<b>Total protein (g/L)</b>				
N	10	10	9	9

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Mean (SD)	71.9 (4.6)	70.5	69.7 (4.9)	-2.3 (3.0)
Median	72	69.5	70	-2.0
Range	65-79	70.5-81	63-78	-7.3 – 3.0
<b>Albumin</b> (g/L)				
N	10	10	9	9
Mean (SD)	43.1 (2.6)	43.2 (2.7)	43.9 (1.8)	0.9 (2.8)
Median	43	43.3	43	0.0
Range	39-47	39 -48	42-47	-3.1 – 5.0
<b>Alk. Phosphatase</b> ( $\mu$ kat/L)				
N	10	10	9	9
Mean (SD)	4.0 (1.6)	5.8 (2.2)	6.7 (2.8)	2.4 (1.5)
Median	4.3	5.5	7.1	1.9
Range	1.9-7.2	2.8-9.4	3.0-11.5	0.3-4.4

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 2, Report # 2).

## Liver Function Tests

### Cohort # 1

Descriptive statistics for liver function tests (total bilirubin, AST, ALT) and LDH are presented in Table 19. These were no clinically meaningful changes in mean values through Month 12.

The applicant states that “Liver function tests were minimally changed during treatment, with no increases in mean liver enzyme levels.”

**Table 19: Bilirubin, AST, ALT and LDH in Cohort # 1 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Month 12	Change from baseline to Month 12
<b>Total Bilirubin</b> ( $\mu$ mol/L)					
N	17	13	14	13	13
Mean (SD)	6.18 (3.1)	8.3 (6.1)	7.9 (4.0)	7.2 (3.8)	1.56 (3.5)
Median	5.0	5.9	6.3	6.8	2.0
Range	3.4-15	3.7-25	3.4-18	3.9-19	-6.1-9
<b>AST</b> ( $\mu$ kat/L)					
N	17	12	15	14	14
Mean (SD)	0.6 (0.09)	0.6 (0.1)	0.6 (0.1)	0.5 (0.08)	-0.09 (0.07)
Median	0.6	0.5	0.5	0.5	-0.09
Range	0.48-0.8	0.4-1	0.4-1.2	0.3-0.6	-0.2-0.05
<b>ALT</b> ( $\mu$ kat/L)					
N	19	16	16	15	15
Mean (SD)	0.33 (0.08)	0.3 (0.1)	0.3 (0.1)	0.2 (0.07)	-0.03 (0.1)
Median	0.3	0.3	0.2	0.2	-0.02

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Range	0.2-0.5	0.2-0.6	0.2-0.9	0.1-0.4	-0.2-0.1
<b>LDH</b> ( $\mu$ kat/L)					
N	16	7	13	11	11
Mean (SD)	8.0 (2.5)	7.4 (2.8)	8.5 (3.0)	8.2 (2.6)	-0.49 (1.7)
Median	8.4	7.9	9.1	8.9	-0.3
Range	4-11.3	2-12	3.9-12.4	4.2-11.6	-4.5-2.0

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 1, Report # 2).

## Cohort # 2

Descriptive statistics for liver function tests (total bilirubin, AST, ALT) and LDH are presented in Table 20. These were no meaningful changes in mean values through Month 6. The applicant also states that “Mean AST, ALT, and LDH levels showed minimal change from baseline to Month 6.” “Mean total bilirubin decreased slightly whereas total protein and albumin levels were essentially unchanged during the study.”

**Table 20: Bilirubin, AST, ALT and LDH (mean and change from baseline) for Cohort # 2 (Safety Population)**

Analyte (descriptive statistics)	Baseline	Month 3	Month 6	Change from baseline to Month 6
<b>Total Bilirubin</b> ( $\mu$ mol/L)				
N	10	5	9	9
Mean (SD)	6.7 (5.4)	7.7 (2.8)	5.7 (3.6)	-1.15 (6.9)
Median	5.1	7.5	5.4	1.03
Range	2.5-21	4-11	2-14.3	-10-4.6
<b>AST</b> ( $\mu$ kat/L)				
N	10	9	8	8
Mean (SD)	0.7 (0.2)	0.9 (0.5)	0.66 (0.1)	-0.07 (0.1)
Median	0.68	0.87	0.65	-0.06
Range	0.43-1.1	0.4-2.1	0.3-0.9	-0.33-0.14
<b>ALT</b> ( $\mu$ kat/L)				
N	10	9	9	9
Mean (SD)	0.3 (0.09)	0.5 (0.5)	0.3 (0.1)	0.05 (0.1)
Median	0.33	0.3	0.3	0.06
Range	0.2-0.4	0.2-1.8	0.2-0.5	-0.13-0.2
<b>LDH</b> ( $\mu$ kat/L)				
N	5	9	8	4
Mean (SD)	8.9 (1.9)	9.1 (1.6)	9.5 (2.4)	0.2 (1.8)
Median	8.9	9.1	9.8	-0.35
Range	5.9-11.1	5.6-11.6	4.7-12.6	-1.1-2.9

Source: Appendix 14.3.4.1 in Clinical; Study Report (Cohort # 2, Report # 2).

## Urinalyses

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### Cohort # 1

There were no clinically meaningful changes in mean values for specific gravity, pH, and percent of subjects with changes in urinalysis components such as protein, red blood cells, glucose, nitrites. The applicant states that

Most urinalysis parameters were unchanged during the study. Urine protein was positive in 1 of 15 subjects at baseline (who was subsequently negative) and 5 of 12 subjects at Month 6, all with trace or minimal protein; a lower incidence was noted at Months 9 and 12. Urine glucose was positive in 0 of 15 subjects at baseline, 2 of 13 at Month 3, and in no subjects at Months 6, 9, or 12. Urine ketones were present in 1 subject at baseline, 3 subjects at Months 3 and 6, and fewer subjects thereafter. Urine blood was detected in 3 of 16 subjects at baseline, 5 of 12 subjects at Month 6, and 4 of 15 subjects at Month 12.

### Cohort # 2

It is reported that “urinalysis parameters were essentially unchanged during treatment in Cohort #2.”

## Hormone testing

Thyroid function testing was performed at Screening and every 6 months during the trial. Protocol Amendment 4 added testosterone and estradiol and changed “T4” to “free T4.”

### Cohort # 1

The applicant reports that “TSH values tended to decrease during treatment” but “no subjects were reported with hypothyroidism or hyperthyroidism.” Testosterone and estrogen measurements “were not clinically abnormal.”

## **Cohort # 2**

The applicant describes a “decrease in mean TSH levels” as was seen in Cohort #1. One subject (9302-204) was diagnosed with hypothyroidism at Month 3 and treated with levothyroxine.

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

## **Cohort # 1**

### **Hematology**

The applicant reports that “several subjects in the study had low hematocrit and/or hemoglobin levels at baseline and/or during the study” and that “two subjects developed high eosinophil counts at Month 6, as did 3 subjects at Month 12.”

#### **Reviewer’s observations:**

This reviewer did not identify in the dataset any “high” hemoglobin values (Appendix 16.2.8.3, Cohort #1). Several patients had hemoglobin concentrations reported as “low” at screening, baseline and subsequent visits.<sup>93</sup> The lowest hemoglobin value on trial

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<sup>93</sup> 7/17 (41.2 %) subjects at screening, 6/16 (37.5%) at baseline, 8 /17 (47 %) on Day 4, 7/17 (41 %) at Month 1, 10/18 (55%) at Month 3, 10/18 (55%) at Month 6, 6/16 (37%) at Month 9, and 6/15 (40%) at Month 12.

was 8.9 g/dL at Month 9 (subject 8805-115) and was followed by a normalized hemoglobin of 10.5 g/dL at Month 12. There were no other hemoglobin measurements below 9 g/dL reported.

There were only a few isolated measurements of platelet counts above and below the normal range.<sup>94</sup> Occasional elevations in platelet counts of no clinical relevance were observed.

There were no clinically relevant reductions or elevations in the total white count.<sup>95</sup>

Eosinophilia was reported in several patients at various times during the trial.<sup>96</sup>

## Sodium

Reviewer's observations:

There were no reports of hyponatremia in the Appendix 16.2.8.2 dataset. Several patients had below normal serum sodium levels on one or more occasions; most were minimal and isolated deviations.<sup>97</sup>

## Potassium

There were no potassium measurements over 5 mmol/L. A few potassium measurements were below the lower limit of normal, most of them isolated findings.<sup>98</sup>

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<sup>94</sup> The following below normal platelet counts were reported; 123,000/mm<sup>3</sup> (subject 7601-107, isolated finding, subsequently normalized), 135,000/mm<sup>3</sup> and 49,000/mm<sup>3</sup> (subject 8803-113, isolated findings, both subsequently normalized).

<sup>95</sup> There was one measurement of total white count below the lower limit of normal (4,500/mm<sup>3</sup> with normal absolute neutrophil count) which was normalized on subsequent measurements. Several observations of increased white cell count were recorded, none of clinical significance.

<sup>96</sup> 4/17 (35%) at screening, 3/14 (21%) at baseline, 8/17 (47%) on Day 4, 4/15 (26%) at Month 1, 5/17 (29%) at Month 3, 5/18 (27%) at Month 6, 7/16 (43%) at month 9, and 7/14 (50%) at Month 12. The applicant reports that "two subjects developed high eosinophil counts at Month 6, as did 3 subjects at Month 12; mean absolute eosinophil counts did not change from baseline."

<sup>97</sup> The lowest sodium serum concentration was 132 mmol/L at Month 12, an isolated finding for patient 8501-116.

<sup>98</sup> Patient 7202-118 had a potassium level of 3.3 mmol/L at baseline; patient 7301-110 had potassium levels of 3.4

### Chloride

There were no measurements in the hypochloremic range. Several patients had occasional above-normal chloride measurements (range 108 to 113 mmol/L). They were almost invariably isolated findings.<sup>99</sup>

### Magnesium

There were no above-normal measurements of serum magnesium. There was only one borderline below-normal magnesium measurement.

### Calcium

Above normal serum calcium concentrations were observed in 3 patients; below normal calcium serum concentrations were present in two patients. All out-of-range measurements were of no clinical significance.

### Phosphate

Elevations in serum phosphate levels were seen in approximately 1/2 to 1/3 of subjects at various visits.<sup>100</sup> The applicant states that "Month 12 shift table analysis [...] revealed increases to above normal serum phosphate levels in several subjects; mean serum phosphate levels changed minimally from 1.5 mmol/L at baseline (n=17) to 1.7 mmol/L at Month 6 (n=14) and 1.6 mmol/L at Month 12 (n=13).

The phosphate measurements below the lower limit of normal are illustrated in Table 21:

**Table 21: Below Normal Measurements of Serum Phosphate in Cohort # 1- Safety Population**

Pt. ID	Visit	Measurement (mmol/L)	Normal Range (mmol/L)	Comments
7301-110	Month 1	1.1	1.3-2	Normal subsequent values.
7801-103	Day 4	0.8	1-2	Normal subsequent value.

and 3.6 mmol/L at Month 1 and Month 3 respectively with normal subsequent levels; patient 7801-103 had a potassium level of 3.3 mmol/L on Day 4 (normal subsequently); patient 8501-116 had a potassium level of 3.2 mmol/L at Month 12 (normal levels previously); patient 8702-109 had three abnormal potassium measurements of 3.7 mmol/L (baseline), 3.5 mol/L at Month 1, and 3.2 mmol/L at Month 6 (normal subsequent levels); five additional patients ( 8801-111, 8802-112, 8803-113, 8804-114 and 8805-115) had several borderline low potassium levels (normal in most of other measurements).

<sup>99</sup> One patient (8201-101) had four such measurements (between 108 and 111 mmol/L) which were all associated with normal sodium and potassium concentrations for the corresponding timepoints.

<sup>100</sup> 2/15 (13%) subjects at screening, 4/17 (23%) at baseline, 3/14 (21%) on Day 4, 5/16 (31%) at Month 1, 8/14 (57%) at Month 3, 10/16 (62%) at Month 6, 7/14 (50%) at Month 9 and 5/13 (38%) at Month12.

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8501-116	Screening	1.1	1.3 – 1.75	Normal measurements at Months 3, 6 and 9.
8501-116	Day 4	1.2	1.3 – 1.75	See above.
8501-116	Month 1	1.2	1.3 – 1.75	See above.
8501-116	Month 12	0.9	1.3 – 1.75	See above.

Source: Appendix 13.2.8.2 and 16.2.8.8

## Creatinine

There were no measurements of elevated serum creatinine levels.

## BUN

Above-normal BUN values are displayed in Table 22; most values were minimal increases above the normal range and all were associated with normal creatinine serum concentrations.

**Table 22: Above Normal Measurements of Serum Blood Urea Nitrogen in Cohort # 1- Safety Population**

Pt. ID	Visit	Measurement mmol/L (mg/dL)	Normal Range mmol/L or mg/dL	Comments
7201-117	Month 9	5.96 (NA)	1.4-5.7 mmol/L	All previous measurements in normal range.
7401-119	Baseline	9.0 (25.1)	5-20 mg/dL*	All other measurements in normal range.
8202-102	Screening	7.7 (NA)	2.5-7.5 mmol/L	All other measurements in normal range.
8801-111	Screening	7.1 (20)	5-18 mg/dL**	All other measurements in normal range.
8804-114	Baseline	8.6 (24)	5-18 mg/dL***	All other measurements in normal range.
8805-115	Baseline	8.2 (23)	5-18 mg/dL#	Most values on trial normal.
8805-115	Month 3	6.8 (19)	5-18 mg/dL##	See above.

Source: Appendix 13.2.8.2 and 16.2.8.8 NA = not abailable.

\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (9.0) and mg/dL (25.1).

\*\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (7.1) and mg/dL (20).

\*\*\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (8.6) and mg/dL (24).

#Normal range presented in mg/dL. Actual measurement presented both as mmol/L (8.2) and mg/dL (23).

##Normal range presented in mg/dL. Actual measurement presented both as mmol/L (6.8) and mg/dL (19).

## Uric Acid

There were no above-normal uric acid values. Several patients had below-normal values at various times on trial.<sup>101</sup>

## Glucose

Below normal glucose levels were reported in 4/14 (28%) patients at screening, 6/15 (40 %) at baseline, 1/12 (8.3 %) on Day 4, 3/14 (21%) at Month 1, 1/14 (7%) at Month 3, 3/15 (20%) at Month 6, 2/16 (12%) at Month 9, and 3/12 (25 %) at Month 12. A few patients had above

<sup>101</sup> 2/13 (15%) patients at screening, 3/14 (21%) at baseline, 8/11 (72%) on Day 4, 6/13 (46%) at Month 1, 6/10 (60%) at Month 3, 7/12 (50%) at Month 6, 6/13 (46%) at Month 9 5/14 (35%) at Month 12.

normal glucose values recorded on trial.<sup>102</sup> The below normal glucose values are highlighted in Table 23. The applicant states that

“Individual capillary glucose values pre- and on-treatment were all 49 mg/dL or greater except on day 4 pre-breakfast, when Subject 8803-113 had a pre breakfast value of 38 mg/dL.” “Low serum glucose values were seen at Month 6 in 3 subjects who also had low values at baseline. Low serum glucose was also reported in 2 subjects at Month 9 and 3 subjects at Month 12.”

**Table 23: Below Normal Measurements of Serum Glucose in Cohort # 1- Safety Population**

Pt. ID	Visit	Measurement mmol/L (mg/ml)	Normal Range mmol/L (mg/ml)	Comments
7201-117	Screen.	2.9 (NA)	3.3-5.6	Normal or above-normal subsequent values.
7401-119	Baseline	3.3 (60)	NA (70-110)*	All other values normal.
7502-106	Month 12	4.1 (74)	NA (78-115)**	Most values missing (normal   at Month 9)
7901-104	Month 9	2.9 (NA)	3.1-6.1	All other values normal.
8701-108	Month 9	2.8 (50)	NA (60-110)***	All other values normal.
8801-111	Screen.	3.8 (68)	NA (70-110)^	Normal at Day 4, Months 9 and Month 12.
8801-111	Baseline	3.4 (61)	NA (70-110)^^	Normal at Day 4, Months 9 and Month 12.
8801-111	Month 1	3.7 (66)	NA (70-110)^^^	Normal at Day 4, Months 9 and Month 12.
8801-111	Month 3	3.7 (66)	NA (70-110)^^^	Normal at Day 4, Months 9 and Month 12.
8801-111	Month 6	3.3 (60)	NA (70-110)*	Normal at Day 4, Months 9 and Month 12.
8802-112	Screen.	3.4 (61)	NA (70-110)^^	Normal at Months 3 through Month 9.
8802-112	Baseline	3.7 (67)	NA (70-110)#	Normal at Months 3 through Month 9.
8802-112	Day 4	3.1(55)	NA (70-110)###	Normal at Months 3 through Month 9.
8802-112	Month 1	1.3 (23)	NA (70-110)###	Normal at Months 3 through Month 9.
8803-113	Baseline	3.7 (66)	NA (70-110)^^^	Normal values at Day 4, Months 1, 3 and 9.
8803-113	Month 6	3.8 (68)	NA (70-110)''	Normal values at Day 4, Months 1, 3 and 9.
8803-113	Month 12	3.6 (64)	NA (70-110)''''	Normal values at Day 4, Months 1, 3 and 9.
8804-114	Baseline	3.7 (67)	NA (70-110)#	All other values normal.
8805-115	Screen	2.8 (50)	NA (70-110)***	Normal values at Day 4, Months 3, and 12.
8805-115	Baseline	3.7 (67)	NA (70-110)#	Normal values at Day 4, Months 3, and 12.
8805-115	Month 1	3.7 (66)	NA (70-110)^^^	Normal values at Day 4, Months 3, and 12.
8805-115	Month 6	3.1 (56)	NA (70-110)''''''	Normal values at Day 4, Months 3, and 12.
8805-115	Month 9	3.8 (69)	NA (70-110)@	Normal values at Day 4, Months 3, and 12.

Source: Appendix 13.2.8.2 and 16.2.8.8 NA = not available in the submission source.

\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.3) and mg/dL (60).

\*\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (4.1) and mg/dL (74).

\*\*\* Normal range presented in mg/dL. Actual measurement presented both as mmol/L (2.8) and mg/dL (50).

^ Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.8) and mg/dL (68).

^^ Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.4) and mg/dL (61).

^^^ Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.7) and mg/dL (66).

# Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.7) and mg/dL (67).

## Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.1) and mg/dL (55).

### Normal range presented in mg/dL. Actual measurement presented both as mmol/L (1.3) and mg/dL (23).

<sup>102</sup> 2/12 (16%) patients on Day 4, 2/14 (14%) at Month 1, 3/14 (21%) at Month 3, and 1/15 (6%) at Month 6. There were no above normal glucose values at screening, baseline, Month 9 and Month 12.

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“Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.8) and mg/dL (68).

““Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.6) and mg/dL (64).

“““Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.1) and mg/dL (56).

@ Normal range presented in mg/dL. Actual measurement presented both as mmol/L (3.8) and mg/dL (69).

Above normal glucose concentrations are listed in Table 24.

**Table 24: Above Normal Measurements of Serum Glucose in Cohort # 1- Safety Population**

Pt. ID	Visit	Measurement in mmol/L	Normal Range (umol/L)	Comments
7201-117	Day 4	6.0	3.3-5.6	Normal values at baseline and Months 9 and 12.
7201-117	Month 1	6.7	3.3-5.6	Normal values at baseline and Months 9 and 12.
7201-117	Month 3	7.0	3.3-5.6	Normal values at baseline and Months 9 and 12.
7202-118	Day 4	6.6	3.3-5.6	Normal values at baseline and Months 6, 9 and 12.
7202-118	Month 1	5.9	3.3-5.6	Normal values at baseline and Months 6, 9 and 12.
7202-118	Month 3	7.3	3.3-5.6	Normal values at baseline and Months 6, 9 and 12.
7601-107	Month 3	8.34	3.3-5.6	Nl. values at baseline, Month 1; missing values at Month 9 and 12.
7601-107	Month 6	6.2 2	3.3-5.6	See above.

### Albumin/Total protein

There were few out of range (borderline high and borderline low) measurements for total protein and albumin.

### Alkaline phosphatase

There were several above-normal measurements at various timepoints. None was > 2X ULN.<sup>103</sup>

### Total bilirubin

The vast majority of total bilirubin values were within normal range.<sup>104</sup>

### ALT

A few patients had elevated ALT levels.<sup>105</sup> Elevated ALT values are presented in Table 25. There was one isolated measurement that was > 2X ULN (patient 7601-107, at Month 1; this

<sup>103</sup> 2/16 (12.5%) at screening, 3/17 (17%) at baseline, 2/16 (12%) on Day 4, 4/18 (22%) at Month 1, 3/16 (18%) at Month 3, 5/18 (27%) at Month 6, 2/14 (14%) at Month 9, and 0/12 (0%) at Month 12.

<sup>104</sup> There was a single bilirubin measurement above the upper limit of normal in patient 7801-103 at the Day 4 visit: 28.0 µmol/L (normal range 3-25 µmol/L). None of the other measurements for this or any other patients were abnormally high.

<sup>105</sup> 0/17 (0%) at screening, 1/18 (5%) at baseline, 2/17 (11%) on Day 4, 1/15% (6%) at Month 1, 1/16 (6%) at Month 3, 3/17% (17%) at Month 6, 0/16% (0%) at Month 9, and 0/12 (0%) at Month 12.

patient had normal ALT values at screening, baseline, Month 3 but not at Day 4 and Month 6, which was the last measurement on trial; see also SAE Section 7.1.2).

**Table 25: Above Normal Measurements of Serum ALT in Cohort # 1- Safety Population**

Pt ID	Visit	Actual Value in $\mu\text{kat/L}$ and (U/L)	Normal Range	X ULN	Comments
7201-117	Day 4	0.80 (48)	<40 IU	<2	Isolated finding. Normal prior (2) and subsequent (4) values. NI. bilirubin.
7601-107	Day 4	0.43 (NA)	0.08-0.42 $\mu\text{kat/L}$	< 2	Normal at baseline and Month 6; bilirubin normal.
7601-107	Mo 1	0.98 (NA)	0.08-0.42 $\mu\text{kat/L}$	> 2	Normal at baseline and Month 6; bilirubin normal.
7601-107	Mo 6	0.50 (NA)*	0.08-0.42 $\mu\text{kat/L}$	< 2	Normal at baseline and Month 6; bilirubin normal..
8501-116	Base.	0.45 (27)	10-25 U/L	<2	Normal values on Day 4, Month 1, 3, 9 and 12.
8501-116	Mo 6	0.53 (32)	10-25 U/L	<2	Normal values on Day 4, Month 1, 3, 9 and 12.
8702-109	Mo 3	0.62 (37)	10-35 U/L	<2	Normal baseline, Months 1, 9 and 12 values.
8702-109	Mo 6	0.90 (54)	10-35 U/L	<2	Normal baseline, Months 1, 9 and 12 values.

\* Last value on trial.

## AST

A relatively large proportion of patients had AST elevations at various points during the clinical trial.<sup>106</sup> Only two measurements were >2X ULN (patients 8702-109 and 8805-115) and none was > 3X ULN. Patient 8702-109 had AST elevations from screening through Month 9 but a normal AST at Month 12. Patient 8805-115 had AST elevations from screening through Month 12 with the exception of the Month 6 measurement.

## LDH

Several patients had elevated LDH values at various timepoints during the trial.<sup>107</sup> None of the measurements were >2X ULN. Several patients missed occasional measurements, a few missed all LDH evaluations. The applicant states that “several subjects had slight elevations of AST and LDH at baseline and during study, whereas ALT and bilirubin levels were generally within normal limits.”

<sup>106</sup> 6/15 (40%) at screening, 8/16 (50%) at baseline, 6/15 (40%) on Day 4, 7/14 (50%) at Month 1, 6/12 (50%) at Month 3, 4/16 (25%) at Month 6, 5/14 (35%) at Month 9, and 4/14 (28%) at Month 9.

<sup>107</sup> 7/11 (63%) patients at screening, 5/12 (41%) at baseline, 6/11 (54%) on Day 4, 5/11 (45%) at Month 1, 2/5 (40%) at Month 3, 7/12 (58%) at Month 6, 6/8 (75%) at Month 9, and 6/11 (54%) at Month 12.

## **Cohort # 2**

### **Hematology**

#### Reviewer's observations:

Overall there were no clinically relevant out of range hematology values. The highest hemoglobin value was 14.4 g/dL (upper limit of normal 14.1 g/dL; Appendix 16.2.8.3, Cohort #2 dataset). As noted in Cohort # 1 several subjects had below normal hemoglobin levels at various times during trial.<sup>108</sup> The lowest hemoglobin on trial was 8.2 g/dL in patient 9101-210 on Day 4 of the trial (normalized subsequently) and in patient 9301-203 (also improved on subsequent measurements). There were four hemoglobin measurements in four patients which were less than 9 g/dL. There were no platelet counts below the lower limit of normal; several platelet count elevations were observed, none of clinical relevance. There were no reports of neutropenia and there were no white cell count elevations of clinical significance. Eosinophilia was reported in several patients at various times during the trial.<sup>109</sup>

### **Sodium**

#### Reviewer's observations:

There were no reports of hypernatremia in the Appendix 16.2.8.2 dataset. Several patients had below normal serum sodium levels on one or more occasions (most of them represent minimal and isolated deviations from the normal range).<sup>110</sup>

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<sup>108</sup> 4/8 (50%) subjects at screening, 2/5 (40%) at baseline, 2/4 (50%) on Day 4, 7/9 (77%) at Month 1, 6/9 (66 % at Month 3), and 7/9 (77 %) at Month 6.

<sup>109</sup> 0/8 (0%) subjects at screening, 1/5 (20%) at baseline, 1/4 (25 %) on Day 4, 2/9 (22 %) at Month 1, 1/9 (11%) at Month 3 and 2/9 (22%) at Month 6.

<sup>110</sup> The lowest sodium serum concentration were: 132 mmol/L at baseline in patient 9301-203, 133 mmol/liter and 133 mmol/liter in patient 9302-204 at Month 1 and Month 3 (normal at Month 6), and 133 mmol/liter at baseline in patient 9303-205.

## Potassium

There were no potassium measurements over 5 mmol/L. There were no below normal potassium measurements. The applicant reports that "one subject had elevated potassium levels at both time points."

## Chloride

Several subjects had several above- and below-normal measurements, all isolated findings.<sup>111</sup>

## Magnesium

There were no above-normal measurements of serum magnesium. There was only one borderline below-normal magnesium measurement.

## Calcium

There was one isolated below-normal calcium measurement<sup>112</sup> and two above-normal measurements of no clinical relevance.

## Phosphate

Four patients had above normal phosphate concentrations (highest value on trial 2.2 mmol/L). One patient had a low measurement at screening but normal baseline and on-trial phosphate concentrations.

## Creatinine

There were no measurements of elevated serum creatinine levels.

## BUN

There were only two above-normal BUN measurements in one single patient at screening and baseline which were followed by normal values for the duration of the trial.

## Uric Acid

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<sup>111</sup> The lowest measurement: 94 mmol/L; the highest measurement 114 mmol/L; most measurements were of no clinical significance.

<sup>112</sup> 7.5 mg/dL in patient 9101-210; all other measurements for this patient were within the normal range.

There were no above-normal uric acid values. Many patients had below normal uric acid measurements.<sup>113</sup>

## Glucose

Below normal glucose values are highlighted in Table 25.<sup>114</sup> The applicant states that

“three subjects had low serum glucose levels at baseline and during the study. Two subjects developed a low glucose during the study: Subject 9301-203 had a low serum glucose at Month 1, and reported an adverse event of mild hypoglycemia at Month 5. Subject 9302-204 had a low serum glucose at Month 6 and had previously reported symptomatic hypoglycemia during the first month.”

**Table 26: Below-Normal Measurements of Serum Glucose in Cohort # 2- Safety Population**

Pt. ID	Visit	Measurement in mmol/L (mg/dL)	Normal Range	Comments
8806-208	Screen	3.8 (68)	70-110 mg/dL	Normal values at Months 3 and 6.
8806-208	Baseline	2.7 (49)	70-110 mg/dL	Normal values at Months 3 and 6.
8806-208	Day 4	3.0 (54)	70-110 mg/dL	Normal values at Months 3 and 6.
8806-208	Month 1	3.2 (57)	70-110 mg/dL	Normal values at Months 3 and 6.
8807-209	Screen.	3.8 (68)	70-110 mg/dL	Normal values at Day 4 and Month 3.
8807-209	Baseline	3.4 (62)	70-110 mg/dL	Normal values at Day 4 and Month 3.
8807-209	Month 1	3.1 (56)	70-110 mg/dL	Normal values at Day 4 and Month 3.
8807-209	Month 6	2.8 (51)	70-110 mg/dL	Normal values at Day 4 and Month 3.
9101-210	Screen	1.8 (32)	70-110 mg/dL	Normal values at baseline and Month 1.
9101-210	Day 4	3.8 (67.8)	70-110 mg/dL	Normal values at baseline and Month 1.
9101-210	Month 6	3.2 (58)	70-110 mg/dL	Normal values at baseline and Month 1.
9301-203	Month 1	2.7 (49)	70-105 mg/dL	All other values normal.
9302-204	Month 6	3.6 (64)	70-105 mg/dL	Normal previous values.
9304-206	Screen.	3.6 (65)	70-105 mg/dL	Normal subsequent values.

A few subjects had occasional above normal glucose measurements. They are highlighted in Table 27.

**Table 27: Above-Normal Measurements of Serum Glucose in Cohort # 2- Safety Population**

Pt. ID	Visit	Measurement in mmol/L (and mg/dL)	Normal Range	Comments
9101-210	Month 3	6.3 (114.3)	70-110 mg/dL	Isolated finding.

<sup>113</sup> 3/9 (33%) patients at screening, 3/4 (75%) at baseline, 4/4 (100%) on Day 4, 3/4 (75%) at Month 1, 5/5 (100%) at Month 3, and 7/8 (87%) at Month 6.

<sup>114</sup> One subject, 9401-207, did not have any glucose measurements.

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9303-205	Month 3	6.3 (114)	70-105 mg/dL	Isolated finding.
9304-206	Month 1	9.9 (178)	70-105 mg/dL	Isolated finding.

### Total protein/ Albumin

There were few out of range (borderline high and borderline low) measurements for total protein and albumin.

### Alkaline phosphatase

There were several measurements above the upper limit of normal at different timepoints.<sup>115</sup> Five measurements in 4 patients were >2X ULN; all were, however, < 3X ULN.

### Total bilirubin

The vast majority of total bilirubin values were within normal range.<sup>116</sup>

### ALT

There were only a few ALT measurements above the upper limit of normal during the trial.<sup>117</sup> They are presented in Table 28. Two patients had ALT elevations >2X ULN: patient 8301-211 and patient 8806-208. Patient 8301-211 had normal ALT measurements at screening, baseline, Day 4, Month 1, but not at Month 3 (last measurement on trial). Patient 8806-208 had normal ALT measurements at screening, baseline, Day 4, and Month 6 but not at Month 1, Month 3. Both discontinued temporarily the treatment (1 ½ month and 10 days, respectively).<sup>118</sup>

<sup>115</sup> 4/9 (44%) at screening, 0/6 (0%) at baseline, 0/4 (0%) on Day 4, 4/9 (44%) on Month 1, 6/10 (10%) on Month 3, and 7/9 (77%) at Month 6.

<sup>116</sup> There was a single bilirumin measurement above the upper limit of normal in patient 7701-201 at baseline: 21.0 µmol/L (normal range < 20 µmol/L). None of the other measurements for this or any other patients were abnormally high.

<sup>117</sup> 1/9 (11%) at screening, 0/6 (0%) at baseline, 0/4 (0%) on Day 4, 2/9 (22%) at Month 1, 3/9 (33%) at Month 3, and 1/9 (11%) at Month 6.

<sup>118</sup> The applicant describes these two subjects as follows "Subject 8301-211 had normal AST and ALT at baseline and Month 1, but moderately elevated at Month 3. She had been on 1.0 mg/kg daily for 2 months followed by 2.0 mg/kg for 1 month. LDH was increased in this subject at baseline and remained unchanged during treatment. At the time of increased transaminases at Month 3, the investigator noted that the patient had been treated with an antibiotic for an upper respiratory infection approximately 10 days prior to the visit, which could have played a role. Study medication was interrupted at that time. Follow up lab results approximately one month later showed that AST and ALT had returned to normal and study drug was restarted after the 6-week interruption. The subject was not compliant with the protocol, discontinued treatment a short time later, and has not yet returned for the Month 6 visit. Subject 8806-208 had borderline elevated AST at baseline and elevation of AST and ALT at the Month 1 visit while receiving study drug at 1.0 mg/kg daily. This subject also reported an upper respiratory infection a few days prior to the Month 2 study visit. Study drug was interrupted for 10 days, after which the levels had returned almost to baseline. Three weeks later, dose was increased to 1.5 mg/kg daily. Enzyme levels increased slightly after restarting treatment, after which they returned to normal levels where they have remained while on treatment. Some of the variability in this subject may be attributable to the use of three different laboratory testing locations. Liver size decreased on ultrasound from baseline to Month 6."

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**Table 28: Above Normal Measurements of Serum ALT in Cohort # 2- Safety Population**

Pt ID	Visit	Actual Value in $\mu$ kat/L and (U/L)	Normal Range	X ULN	Comments
7701-201	Screen.	0.53 (32)	1-25 U/L	< 2	Nl. value at baseline (all other values on trial elevated). No screening bilirubin but bilirubin barely elevated at baseline: 21 (nl < 20 $\mu$ mol/L) and nl. afterwards.
7701-201	Mo 3	0.43 (26)	1-25 U/L	< 2	Nl. value at baseline (all other values on trial elevated). No screening bilirubin but bilirubin barely elevated at baseline: 21 (nl < 20 $\mu$ mol/L) and nl. afterwards.
7701-201	Mo 6	0.52 (31)	1-25 U/L	< 2	Nl. value at baseline (all other values on trial elevated). No screening bilirubin but bilirubin barely elevated at baseline: 21 (nl < 20 $\mu$ mol/L) and nl. afterwards.
8301-211	Mo 3	1.83 (110)*	< 40 U/L	> 2	Last value on trial (no Month 6 value). Nl. bilirubin.
8806-208	Mo 1	1.35 (81)	5-40 U/L	> 2	Normal value at baseline, Day 4, and Month 6. Nl. bilirubin.
8806-208	Mo 3	0.90 (54)	5-40 U/L	< 2	Normal value at baseline, Day 4, and Month 6. Nl. bilirubin.
9304-206	Mo 1	0.70 (42)	< 41 U/L	< 2	Nl. values at baseline, Months 3 and 6. Some bilirubin values missing but all others nl.

\*No Month 6 value. Screen. = screening. Mo =month.

### AST

Several patients had AST elevations above the upper limit of normal at various timepoints during the trial.<sup>119</sup> Four measurements in four patients were > 2X ULN (patients 7701-201, 8301-211, 8806-208, and 9302-204). Patient 8301-211 had the highest AST elevation: 3.25 X ULN at Month 3 (last measurement on trial; all previous measurements through Month 1, inclusively, were normal). Patient 7701-201 had an AST elevation of 2.4X ULN at baseline, and above-normal (but < 2X ULN) elevations through Month 6. Patient 8806-208 had an AST elevation of 2.2X ULN at Month 1 and elevated AST measurement from screening through Month 6. Patient 9302-204 had an AST elevation of 2.5X ULN at Month 3 and lower AST elevations from screening through Month 6.

### LDH

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<sup>119</sup> 6/9 (66%) patients at screening, 3/6 (50%) at baseline, 2/4 (50%) on Day 4, 6/8 (75%) at Month 1, 7/9 (77%) at Month 3, and 5/8 (62%) at Month 6.

Most patients had elevated LDH values at various timepoints during the trial.<sup>120</sup> Only one measurement was > 2X ULN (patient 9303-205); none was > 3X ULN. Patient 9303-205 had elevated LDH measurements at all evaluations completed (Month 1 through Month 6). The applicant states that “

More than half of the subjects had elevated AST and LDH at baseline and during the study, whereas ALT, which is more specific to the liver, was abnormal in only one subject at baseline and a maximum of three subjects at Month 3.”

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

There were no marked outliers and dropouts for laboratory abnormalities.

#### 7.1.7.4 Additional analyses and explorations

The small size of the dataset does not allow for analyses of dose-dependence and/or time-dependence. The limited data on hypoglycemia from Cohort # 1 suggest that hypoglycemia may occur more frequently at the initiation of the treatment.

#### 7.1.7.5 Special assessments

The finding of ALT elevations in two patients resulting in temporary study drug discontinuation was discussed in Section 7.1.7.3.2.

### 7.1.8 Vital Signs

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

Vital signs were part of the routine baseline and on-trial evaluations during study INSM-101-303.

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

Not applicable (there was no control group).

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<sup>120</sup> 4/4 (100%) at screening, 5/5 (100%) at baseline, 3/4 (75%) on Day 4, 8/8 (100%) at Month 1, 8/9 (88%) at Month 3, and 6/8 (75%) at Month 6.

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

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

#### Cohort # 1

Descriptive statistics of vital signs (heart rate, systolic and diastolic blood pressure) are presented in Applicant's Table 17. The mean measurements were relatively constant over time (there was a small downward trend for heart rate and systolic blood pressure)

**Table 17. Vital Signs**

	Baseline	Month 6	Month 12
<b>Heart Rate (bpm)</b>			
N	19	18	16
Mean	103	103	95
SD	12	11	16
Median	101	102	97
Minimum	88	86	62
Maximum	130	129	120
<b>Systolic Blood Pressure (mm Hg)</b>			
N	17	18	16
Mean	102	98	97
SD	12	10	15
Median	100	96	94
Minimum	81	86	77
Maximum	124	119	128
<b>Diastolic Blood Pressure (mm Hg)</b>			
N	17	18	16
Mean	59	57	58
SD	9	10	12
Median	60	55	56
Minimum	43	44	43
Maximum	74	74	80

as were the standard deviations. The range of measurements did not suggest any outliers.

Source: Clinical Study report, Cohort # 1, Report # 2.

#### Cohort # 2

Descriptive statistics of vital signs (heart rate, systolic and diastolic blood pressure) for this cohort are presented in Table 29, which reformats applicant's Table 19 from the Clinical Study report, Cohort # 2, Report # 2. Overall, vital signs were stable over a six-month period. The range of measurements did not suggest any outliers.

**Table 29: Vital signs in Cohort # 2**

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Vital sign (statistics)	Baseline	Month 6
Heart rate (bpm)		
n	10	9
Mean (SD)	102 (16)	109 (11)
Median	109	110
Minimum	70	90
Maximum	120	122
Systolic Blood Pressure (mm Hg)		
n	10	8
Mean (SD)	101 (11)	101 (8)
Median	100	100
Minimum	84	90
Maximum	120	114
Diastolic Blood Pressure (mm Hg)		
n	10	8
Mean (SD)	59 (6)	63 (7)
Median	60	60
Minimum	50	55
Maximum	70	70

Source: Table 19, Clinical Study report, Cohort # 2, Report # 2.

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

Refer to Section 7.1.8.3.1.

*7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities*

Refer to Section 7.1.8.3.1.

**7.1.8.4 Additional analyses and explorations**

No additional analyses and explorations were provided.

## 7.1.9 Electrocardiograms (ECGs)

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

A 12-lead ECGs was performed at baseline and repeated at Month 6 and at Month 12.

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

Not applicable (there was no control group).

### 7.1.9.3 Standard analyses and explorations of ECG data

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

##### **Cohort # 1**

All 19 patients enrolled in Cohort # 1 had baseline ECGs, which were all reported as normal. Three patients (7201-117, 7601-107, and 7801-103) did not have follow-up ECGs. All other 16 patients had follow-up ECGs at Month 6 and/or Month 12 and all evaluations were reported as normal. No further analyses are provided.

##### **Cohort # 2**

All 10 patients enrolled in Cohort # 2 had baseline ECGs and all were reported as normal. Two patients did not have follow-up ECGs (8301-211 and 9101-210). Eight patients had normal follow up ECGs at Month 6. No further analyses are provided.

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

Refer to section 7.1.9.1.3.1.

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

Refer to section 7.1.9.1.3.1.

#### 7.1.9.4 Additional analyses and explorations

No additional analyses and explorations were provided.

#### 7.1.10 Immunogenicity

##### Cohort # 1

Antibodies to IGF-I, IGFBP3, and IGF-I/IGFBP3 complex were measured with an ELISA assays.<sup>121</sup> The incidence of patients who became antibody positive on treatment at Months 3, 6, 9, and 12 is presented in applicant's Table 15 (all subjects were antibody negative at baseline). The percentage of antibody positive patients at Month 12 was 80 % (anti-IGF-I), 67 % (anti-IGFBP3) and 93 % (anti IGF-I/IGFBP3). Antibodies were first detected by 3 months of treatment. The percentage of patients with anti-IGF-I antibodies increased gradually thereafter (from 44 % to 80 %). In contrast the percentage of patients with anti-IGFBP-3 and anti IGF-I/IGFBP-3 antibodies remained high and relatively constant.

**Table 15. Antibody Incidence (n, %)**

	Baseline	Month 3	Month 6 <sup>1</sup>	Month 9 <sup>1</sup>	Month 12 <sup>1,2</sup>
Anti-IGF-I	0/0 (0%)	8/18 (44%)	11/16 (69%)	12/16 (75%)	12/15 (80%)
Anti-IGFBP-3	0/0 (0%)	13/18 (72%)	14/16 (88%)	11/16 (69%)	10/15 (67%)
Anti-IGF-I/IGFBP-3	0/0 (0%)	17/18 (94%)	15/16 (94%)	15/16 (94%)	14/15 (93%)

<sup>1</sup>Subjects 103 (no samples post Month 3), 107 (stopped treatment prior to Month 6), 119 (stopped treatment prior to Month 6) were not included in the analysis.

<sup>2</sup>Subject 117 (no sample available for Month 12) was not included in the analysis.

The antibody titers for each of the three antibodies are presented in applicant's Table 16. Antibody titers peaked by 6-9 months and declined by 12 months. The predominant antibody subclass was IgG1 (most patients) and IgG4 (2 patients). The applicant reports that there was no negative correlation between the immune titer and the change in height velocity at 6, 9, and 12 months.

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<sup>121</sup> The applicant states that "all antibody assays were ELISAs and are expressed in terms of titer, representing the highest dilution at which antibody detection remained greater than approximately 3-times nonspecific background."

The applicant presents data on 3 subjects whose 3-month and 6-month sera were evaluated for neutralizing antibodies using an in vitro bioassay. These patients were selected on the basis of having the highest overall antibody titer against rhIGF-I/rhIGFBP-3 and a high titer against rhIGF-I and rhIGFBP-3 (Subject 110 at 6 months), the highest overall titer against rhIGF-I (Subject 115 at 6 months), and the second highest titer against rhIGF-I/rhIGFBP-3 but a relatively weak titer against rhIGF-I and rhIGFBP-3 (Subject 119 at 3 months). In all three cases, the samples tested did not inhibit cell growth in vitro at the concentrations tested.

On July 1, 2005 the applicant submitted an additional in vitro analysis conducted on serum samples from six patients at Month 9. The patients were selected on the basis of having the highest titers of anti-rhIGF-I/rhIGFBP-3 at Month 9 (subjects 101, 110, 112 and 114) and having the lowest height velocity change (< 2 cm/yr) at Month 12 (subjects 101, 108, 110 and 113). Two subjects (101 and 110) meet both criteria. The bioassay results were negative for neutralizing antibodies.

**Table 16. Antibody Titer**

	Month 3	Month 6	Month 9	Month 12
<b>Anti-IGF-I (titer)</b>				
N	18	16	16	15
Mean	60	568	823	688
SD	89	1274	1419	1403
Median	0	80	160	160
Minimum	0	0	0	0
Maximum	320	5120	5120	5120
<b>Anti-IGFBP-3 (titer)</b>				
N	18	16	16	15
Mean	48	73	50	40
SD	43	44	45	43
Median	40	80	40	40
Minimum	0	0	0	0
Maximum	160	160	160	160
<b>Anti-IGF-I/IGFBP-3 (titer)</b>				
N	18	16	16	15
Mean	2124	2565	2763	1781
SD	3083	3808	2957	2656
Median	960	1280	1920	640
Minimum	0	0	0	0
Maximum	10240	16000	10240	10240

**Cohort # 2**

The incidence of patients who became antibody positive on treatment at Months 3, and 6 in Cohort # 2 is presented in applicant's Table #17 (this Table includes, for comparison the data obtained with Cohort # 1 at the same timepoints). All patients were antibody-negative at baseline. The percentage of antibody positive patients at 6 months was 11 % (anti-IGF-I), 11 % (anti IGFBP3) and 78 % (anti IGF-I/IGFBP3). This was markedly lower than the observations made in Cohort # 1 in particular with respect to anti-IGF-I and anti-IGFBP-3 antibodies.

**Table 17. Antibody Incidence in Cohorts #1 and #2 (n, %).**

	Cohort #1		Cohort #2		All Cohorts
	Month 3	Month 6 <sup>1</sup>	Month 3	Month 6	Month 6
Anti-IGF-I	8/18 (44%)	11/16 (69%)	0/10 (0%)	1/9 (11%)	12/25 (48%)
Anti-IGFBP-3	13/18 (72%)	14/16 (88%)	3/10 (30%)	1/9 (11%)	15/25 (60%)
Anti-IGF-I/IGFBP-3	17/18 (94%)	15/16 (94%)	6/10 (60%)	7/9 (78%)	22/25 (88%)

<sup>1</sup>Subjects 103 (no samples post Month 3), 107 (stopped treatment prior to Month 6), and 119 stopped treatment prior to Month 6). These were not included in the analysis.

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The antibody titers in Cohort #2 were markedly lower than in Cohort #1 (this occurred despite higher doses used in Cohort # 2 between Months 2 and 6). The Month 6 anti-IGF-I mean titers were 31.5X higher in Cohort # 1 relative to Cohort # 2; similarly, the anti IGFBP-3 titers were 18.2 X higher and the anti-IGF-I/IGFBP-3 titers were 8.5 X higher in Cohort #1 when compared to Cohort # 2.<sup>122</sup> The antibody titers of the three types of antibodies discussed are presented in applicant's Table 18. As noted in Cohort # 1 the predominant form of antibody was of the IgG1 subclass. The applicant reports that there was no negative correlation between the immune titer and the change in height velocity at 6 months.

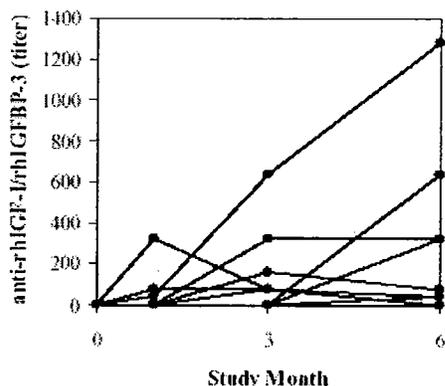
<sup>122</sup> A likely explanation for this observation is the difference in \_\_\_\_\_ between the two drug substances. \_\_\_\_\_ the development drug product manufactured at the Santa Clara facility in California was \_\_\_\_\_ µg/mg in each of the two batches tested and only \_\_\_\_\_ in the Avecia drug substance. Similarly, the amount of \_\_\_\_\_ for the Santa Clara API and \_\_\_\_\_ for the Avecia API.

Table 18. Antibody Titer in Cohorts #1 and #2.

	Cohort #1		Cohort #2	
	Month 3	Month 6	Month 3	Month 6
Anti-IGF-I (titer)				
n	18	16	10	9
Mean	60	568	0	18
SD	89	1274	0	53
Median	0	80	0	0
Minimum	0	0	0	0
Maximum	320	5120	0	160
Anti-IGFBP-3 (titer)				
n	18	16	10	9
Mean	48	73	12	4
SD	43	44	19	13
Median	40	80	0	0
Minimum	0	0	0	0
Maximum	160	160	40	40
Anti-IGF-I/IGFBP-3 (titer)				
n	18	16	10	9
Mean	2124	2565	136	302
SD	3083	3808	203	424
Median	960	1280	80	80
Minimum	0	0	0	0
Maximum	10240	16000	640	1280

Applicant's Figure 13 illustrates the individual titers to the IGF-I/IGFBP3 complex at Months 3 and 6 for patients from Cohort # 2.

Figure 13. Anti-IGF-I/IGFBP-3 Antibody Titer by Study Month in Cohort #2 (n=10)



### 7.1.11 Human Carcinogenicity

There were no reports of malignancies associated with mecasermin rinfabate treatment during Study INSM-110-303. Since IGF-I is a growth factor that plays a central physiologic role in the control of body growth, mecasermin rinfabate treatment in GHIS should be aimed at restoring

physiologic IGF-I levels. Of note, rhIGFBP-3 is currently being investigated as potential anticancer therapy.

#### 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 for rhIGF-I/rhIGFBP-3. Based on our current understanding of the mechanism of action IGF-I and IGFBP-3 there is no theoretical basis to suspect drug dependence for mecaseimerin rinfabate. No drug dependence has been described for somatropin (recombinant human growth hormone), a physiologically related compound with worldwide clinical experience in approximately 200,000 patients.

Since IGF-I has anabolic activity and is responsible for most of GH's anabolic activities, there is a theoretical potential for rhIGF-I/rhIGFBP-3 abuse. The hypoglycemic effect of the product may act as a deterrent for such use.

#### 7.1.14 Human Reproduction and Pregnancy Data

The applicant did not report any pregnancies in the clinical trial.

#### 7.1.15 Assessment of Effect on Growth

Linear growth was an efficacy endpoint for INSM-110-303 clinical study.

#### 7.1.16 Overdose Experience

There were no cases of accidental overdose in clinical trial INSM-110-303. Based on the known insulinomimetic effect of IGF-I it is to be expected that hypoglycemia is the adverse event most likely to occur in cases of accidental overdose with rhIGF-I/rhIGFBP-3.

One accidental overdose due to a nursing error occurred in Study 9701/02 in which a 16-year old with severe burns received 309 mg of rhIGF-I/rhIGFBP-3 instead of a prescribed dose of 15.45 mg for one hour as part of an infusion of the drug. The event did not result in any adverse events or sequelae.

#### 7.1.17 Postmarketing Experience

There is no postmarketing experience with rhIGF-I/rhIGFBP-3.

### 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

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

Refer to Section 6.1.3 for study design and patient disposition.

##### 7.2.1.2 Demographics

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

The exposure to mecaseimerin rinfabate is presented in applicant's Table 13 (Clinical Study Report, Cohort # 2, Report # 2). In Cohort # 1 the mean duration of treatment with rhIGF-I/rhIGFBP-3 was  $11.3 \pm 2.6$  months (range: 3.2 to 12.7 months; total exposure: 215 subject-months). For Cohort # 2, the mean duration of treatment with rhIGF-I/rhIGFBP-3 was  $5.4 \pm 0.8$  months (range: 3.2 to 6.0 months; total exposure: approximately 54 subject-months).

**Table 13. Exposure to Treatments in Cohorts #1 and #2**

	<b>Cohort #1 Safety Population (n=19)</b>	<b>Cohort #2 Safety Population (n=10)</b>	<b>All Cohorts (n=29)</b>
Exposure (months)			
N	19	10	29
Mean	11.3	5.4	9.3
SD	2.6	0.8	3.6
Median	12.1	5.6	12.1
Minimum	3.2	3.2	3.2
Maximum	12.7	6.0	12.7

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

### 7.2.2.1 Other studies

There were no clinical studies with rhIGF-I/rhIGFBP-3 in a pediatric population with similar characteristics as GHIS. RhIGF-I/rhIGFBP-3 has been investigated for several other adult and pediatric indications such as type 1/type 2 diabetes, severe burns, hip fractures, and severe insulin resistance. The exposures in these Phase I/II studies are limited and the safety data cannot be extrapolated to GHIS due to the distinct background of AEs present in these patient populations.

### 7.2.2.2 Postmarketing experience

rhIGF-I/rhIGFBP-3 is not an approved drug in the US.

### 7.2.2.3 Literature

There are no published clinical trials with mecaseimerin rinfabate in GHIS.

## 7.2.3 Adequacy of Overall Clinical Experience

It is important to recognize that GHIS is an extremely rare disease. It has been estimated that the prevalence of Laron Syndrome worldwide is approximately 200-350. The applicant's proposed indication is broader and includes severe short stature associated with a height SD score  $\leq -3$  and IGF-I SDS. This is likely to result in a larger target population but, by current estimates, not larger than 6,000 in the US (and approximately the same in Europe). The 29 patients studied in the mecaseimerin rinfabate clinical program represent approximately 10 % of the Laron syndrome patient population. The duration of exposure is sufficient to demonstrate short-term efficacy. However, there are no efficacy and safety data beyond one year of treatment. This information should be reflected in the label.

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

See pharmtox. review.

#### 7.2.5 Adequacy of Routine Clinical Testing

The safety assessments in clinical trial INSM-110-303 include adverse events, laboratory testing (chemistry, hematology, urinalysis, hormone levels), physical examination (including fundoscopy, injection site evaluations), vital signs, abdominal/pelvic ultrasound, capillary blood glucose, electrocardiogram, echocardiogram, and audiograms. These evaluations were performed at baseline and at different time points during the study. They were, in general, adequate.

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

The basic physiology of IGF-I and IGFBP-3 is well characterized.

#### 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

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

Refer also to section 7.2.5. In general, the applicant assessed appropriately the adverse events expected to occur in association with rhIGF-I/rhIGFBP-3 such as hypoglycemia, tonsillar hypertrophy, organomegaly, allergic reaction, and antibody formation.

#### 7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update included most of the clinical data that are summarized in this review: 12-month data for Cohort # 1 and 6-month data for Cohort # 2. The initial NDA submission had only limited clinical data (6 months of data for Cohort # 1 and 2-months of data for Cohort # 2).

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

Despite the absence of a control group that would perhaps permit differentiation of the adverse events associated with mecasermin rinfabate treatment from background 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 and should be included in the label:

- As expected from the known insulinomimetic mechanism of action of IGF-I and from the published data obtained with rhIGF-I, mecasermin rinfabate can cause hypoglycemia, which occasionally can be severe.
- Hypertrophy/rapid growth of the lymphoid tissues (tonsillar, adenoid, splenic) occurs during mecasermin rinfabate treatment. Secondary complications (chronic middle ear effusions, hearing loss, sleep apnea, and need for tonsillectomy/adenoidectomy) can occur and should be monitored for. They are treatable, should they occur.
- Injection site reactions are frequent and should be explicitly described in the label along with strategies to minimize their occurrence (injection site rotation).
- Although no neutralizing antibodies have been identified to date, a large proportion of patients developed antibodies to the rhIGF-I/rhIGFBP-3 complex. Combined with the fact that the rhIGFBP-3 component of mecasermin rinfabate is not glycosylated (in contrast with the native human IGFBP-3) there is at least a theoretical risk that patients may develop in time neutralizing antibodies. This theoretical risk should be labeled so that practicing physicians investigate promptly any loss of efficacy on treatment.
- As IGF-I is the main mediator of GH actions and since adverse events similar to those described in association with GH treatment have been observed with mecasermin rinfabate even in a small dataset (e.g. arthralgia, hypothyroidism, and papilledema), it is likely that in a larger patient population and with additional patient exposures to mecasermin rinfabate additional GH-associated adverse events will be observed in the future. Therefore, it is prudent to mention this class of adverse events in the mecasermin rinfabate label.
- Two adverse events of ovarian cysts were reported. Although, as for most adverse events causality cannot be demonstrated, ovarian cyst formation is one of the labeled AEs for the rhIGF-I product approved in Japan.
- Since a large proportion of patients had abnormal serum analyte measurements at baseline and at subsequent visits (e.g. AST, LDH) this should be labeled as such.
- Two patients had AST elevations that required temporary interruption of mecasermin treatment (one patient continued the treatment without further incidents, the other was later discontinued from the trial for poor compliance).
- Facial soft tissue changes and mandibular growth have been described in the medical literature in association with long-term rhIGF-I treatment. Therefore, this potential risk should be mentioned in the label.
- Since IGF-I is very close functionally to GH the label should assert clearly that the two drugs are distinct and should not be used to replace each other for approved and labeled indications.
- The label should mention that efficacy and safety beyond one year have not been studied. Importantly, the applicant should further investigate postapproval the theoretical risk of developing neutralizing antibodies.

## 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

Not applicable (there was only one clinical study conducted in patients with GHIS).

#### 7.4.1.2 Combining data

Not applicable since there was only one clinical study conducted in patients with GHIS.

### 7.4.2 Explorations for Predictive Factors

The datasets are too small to conduct additional analyses.

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

Due to the small size of the datasets and the limited exposure no dose dependency analyses were done.

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

Due to the small size of the datasets and the limited exposure no time dependency analyses were done

#### 7.4.2.3 Explorations for drug-demographic interactions

Due to the small size of the datasets and the limited exposure no drug-demographic interactions were analyzed.

#### 7.4.2.4 Explorations for drug-disease interactions

Due to the small size of the datasets and the limited exposure no drug-disease interactions were analyzed.

#### 7.4.2.5 Explorations for drug-drug interactions

Due to the small size of the datasets and the limited exposure no drug-drug interactions were analyzed.

### 7.4.3 Causality Determination

There was no control group in the clinical trial ISM-110-303. Therefore, assigning causality for the adverse events observed is particularly difficult. Several AEs, however, could be linked to mecasermin rinfabate with a reasonable degree of certainty on the basis of the known insulinotropic 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 applicant has investigated two dose regimens in the clinical trial INSM-110-303: 1mg/kg and 2 mg/kg (given as a single subcutaneous injection after the evening meal).<sup>123</sup> Both regimens appear safe and effective if appropriately labeled. The efficacy analysis of height velocity at Month 6 suggests that the higher dose may be associated with a better efficacy response. It is important to recognize, however, that patients were not randomized to the two drug regimens.<sup>124</sup> The small safety dataset available to date does not indicate a clear pattern of dose-dependent adverse events.

The titration regimen brought serum IGF-I levels within the normal range of -2 SD to + 2SD for most patients. Several outlier values were observed including a remarkable one (up to +20 SD). In Cohort # 1 two patients had their rhIGF-I/rhIGFBP-3 doses reduced due to excessive serum IGF-I levels; in Cohort # 2 all patients could be eventually titrated to the 2 mg/kg dose.

### 8.2 Drug-Drug Interactions

No drug interaction studies were conducted.

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<sup>123</sup> The applicant chose the 1 mg/kg dose on the basis of a pharmacokinetic study in children with GHIS, which showed that “administration of 1.0 mg/kg of rhIGF-I/rhIGFBP-3 once daily was comparable to 80 µg/kg of rhIGF-I given twice daily in restoring mean peak IGF-I levels to within the normal range.” rhIGF-I has been given safely in children with GHIS in doses up to 120 µg/kg twice a day and the approved doses for Increlex (rhIGF-I) are 80-120 µg/kg BID.

<sup>124</sup> Patients were assigned somewhat arbitrarily to the low dose regimen of 1mg/kg dose in Cohort # 1 and, following reassuring efficacy and safety results with this dose, a second group of subjects (Cohort # 2) was titrated up to a 2 mg/kg daily dose based on serum IGF-I levels. The titration scheme recommended by the Steering Committee was as follows: if IGF-I SDS on treatment is  $\leq 2$ : increase the daily dose by 1.0 mg/kg (maximum dose 2 mg/kg); if IGF-I SDS is between -2 and 0: increase daily dose by 0.5 mg/kg (maximum dose 2 mg/kg); if IGF-I SDS is between 0 and + 3: do not change the dose; if IGF-I SDS is  $> + 3$  and/or intolerable side effects: decrease the daily dose by 0.5 mg/kg.

### 8.3 Special Populations

The applicant did not conduct formal studies that evaluated the effect of age, gender, race or comorbid states (such as renal or hepatic failure) on mecasermin rinfabate's efficacy and safety.

### 8.4 Pediatrics

Mecasermin rinfabate is intended exclusively for the treatment of \_\_\_\_\_ in pediatric patients with GHIS and open epiphyses. A pediatric waiver should be granted for children less than 3 years of age (children below 3 years of age have not been studied in this clinical trial).

### 8.5 Advisory Committee Meeting

There were no Advisory Committee Meetings for this application.

### 8.6 Literature Review

There are no published clinical trials of rhIGF-I/rhIGFBP-3 in patients with GHIS. There is, however, relatively extensive data concerning short-term and long-term efficacy and safety of rhIGF-I in this patient population. The applicant presents a summary of this information accumulated from 169 patients with Laron syndrome and 13 patients with GH gene deletion and neutralizing antibodies. Briefly, the mean height velocity for the rhIGF-I studies was 3.2 cm/yr pre-treatment, 8.2 cm/yr during Year 1, and 6.2 cm/yr during Year 2. Improvements in mean height SDS of 0.7 to 1.0 were generally seen after 1 year of rhIGF-I therapy with total gains of 1.5 after prolonged treatment. The doses of rhIGF-I used in these studies range between 40-120 µg/kg BID.<sup>125</sup> Table 30 summarizes applicant's Table 6 from Section 2.7.3 (it excludes clinical trial who contributed < 10 patients). The results are comparable across clinical trials; in particular, efficacy data obtained with rhIGF-I/rhIGFBP-3 at 1 mg/kg and standard rhIGF-I doses are comparable.

**Table 30: Summary of efficacy from Studies of rhIGF-I or rhIGF-I/rhIGFBP-3**

	Pharmacia Multicenter	Pharmacia Ecuador	Pharmacia UK/France	Genentech Multicenter	Insmed Multicenter*
No subjects	33	17	11	65	29
GHRD/GH-IA	31/2	17/0	11/0	58/7	25/2
Male/female	17/16	7/10	8/3	39/26	17/12
Pubertal (baseline)	9	0	0	NA	0
Dose	rhIGF-I: 40-120 µg/kg BID	rhIGF-I: 120 µg/kg BID	rhIGF-I: 80 µg/kg BID	rhIGF-I: 60-120 µg/kg BID	rhIGF-I/rhIGFBP-3: 1 mg/kg

<sup>125</sup> A dose of 80 µg/kg BID of rhIGF-I is roughly equivalent to a daily dose of 1 mg/kg of rhIGF-I/rhIGFBP-3 in restoring peak IGF-I levels in the normal range.

Clinical Review  
 {Dragos Roman}  
 {21-884/N000}  
 {Mecasermin rinfabate (iPLEX)}

<b>Baseline age (yr)</b>	11.1	9.8	7.5	6.5	9.0
<b>Height velocity (cm/yr)</b>					
<b>Baseline</b>	3.9	3.4	3.1	2.6	3.4
<b>Year 1</b>	8.2	8.2	7.7	8.0	7.4
<b>Year 2</b>	6.3	6.4	7.0	6.0	
<b>Year 3</b>	5.2	6.0		5.2	
<b>Year 4</b>	4.7				
<b>Height SDS</b>					
<b>Baseline</b>	-6.8	-8.5	-5.5	-6.5	-6.5
<b>Year 1</b>	-6.1	-7.5	-4.9	-5.7	-6.1
<b>Year 2</b>	-5.2	-7.0		-5.4	
<b>Year 4+</b>	-4.9			-5.1	
<b>Bone age</b>					
<b>Year 0-1</b>	1.2	0/8	1.9		0.3
<b>Year 0-2</b>	2.4	2.2			

Source: Summary of Clinical Efficacy, Section 2.7.3. GHRD = GH receptor deficiency. GH-1A = GH gene deletion. NA = not available.

\*Data are presented for the first 6 months with the 1 mg/kg dose.

Table 31 highlights the one-year efficacy data from previous table and updates the data obtained with Cohort # 1 at Month 12 and Cohort # 2 at Month 6.

**Table 31: First year efficacy for rhIGF-I and rhIGFBP-3**

	Pharmacia rhIGF-I 40-120 µg/kg BID	Pharmacia Ecuador rhIGF-I 120 µg/kg BID	Pharmacia UK/France rhIGF-I 80 µg/kg BID	Genentech rhIGF-I 60-120 µg/kg BID	iPLEX		
					Cohort # 1 6 months n=16*	Cohort # 1 12 months n=16*	Cohort # 2 6 months n=9**
<b>Height velocity (cm/yr.)</b>							
Baseline	3.9	3.4	3.1	2.6	3.4 ± 1.9	3.4 ± 1.9	2.2 ± 1.5
Endpoint <sup>^</sup>	8.2	8.2	7.7	8.0	7.4 ± 2.0	6.4 ± 1.6	8.8 ± 2.0
Change	4.3	4.8	4.6	5.4	4.0 ± 1.8	3.0 ± 1.3	6.6 ± 2.6
<b>Height SDS</b>							
Baseline	-6.8	-8.5	-5.5	-6.5	-6.4 ± 2.1	-6.4 ± 2.1	-7.9 ± 1.1
Endpoint <sup>^</sup>	-6.1	-7.5	-4.9	-5.7	-6.1 ± 2.1	-6.0 ± 2.2	-7.5 ± 1.1
Change	0.7	1	0.6	0.8	0.3 ± 0.2	0.5 ± 0.4	0.42 ± 0.25

\* Maximum daily dose: 1.0 mg/kg (mean dose 0.9 mg/kg).

\*\* Maximum daily dose: 2.0 mg/kg (mean dose 1.4 mg/kg).

<sup>^</sup> Month 12 unless otherwise specified.

The applicant provides an additional comparison of the efficacy responses at Month 6 for rhIGF-I/rhIGFBP-3 (1 mg/kg dose) and rhIGF-I (data derived from the Pharmacia Clinical Study 90-111/92-5302-001; this study was the pivotal clinical trial included in the submission for marketing authorization made to the EMEA). The efficacy results are comparable. Specifically, for subjects receiving rhIGF-I, the mean height velocity increased from  $3.8 \pm 1.8$  to  $8.8 \pm 2.9$  cm/yr ( $p < 0.0001$ ). The mean height velocity for subjects who received rhIGF-I/rhIGFBP-3 increased from  $3.4 \pm 1.9$  to  $7.4 \pm 2.0$  cm/yr. Individual responses were also comparable.

The applicant also provides an analysis of the published safety data for 182 subjects treated worldwide with rhIGF-I manufactured by Genentech, Pharmacia, and Fujisawa. In the Summary of Clinical Safety the applicant states the following:

In summary, hypoglycemia has been reported in approximately 40 % of GHIS children treated with rhIGF-I, sometimes severe and requiring medical intervention and /or discontinuation of treatment. Injection site pain and lipohypertrophy at injection sites were also commonly reported. Tonsillar hypertrophy resulted in subjects in several studies undergoing tonsillectomy and adenoidectomy. Middle ear effusions and hearing loss were reported. Cases of intracranial hypertension, with papilledema, headache and nausea, have been reported, as have cases of facial nerve paralysis. Changes in facial features have been documented. Laboratory measurement abnormalities have included hypoglycemia, anemia, hypokalemia, increased urinary calcium, and elevated liver enzymes. Antibodies to IGF-I were detected in the two studies in which this trial was investigated.

The applicant provides an analysis that compares safety findings from the pivotal registration studies of rhIGF-I (Pharmacia clinical study 90-111/92-5302-001) and rhIGF-I/rhIGFBP-3 (INSM-110-303) over a similar duration of exposure (6- months).<sup>126</sup> To ensure an equitable comparison of AEs reported in the two studies, the AEs reported in the rhIGF-I study 90-111/92-5302-001 were recorded under blinded conditions using the same methods and personnel used to code AEs for Clinical Study INSM-110-303. The applicant states the following:

The majority of subjects in Clinical Studies INSM-110-303 and 90-111/92-5302-001 reported an AE during the 6 first six months of treatment. Nineteen (100%) of 19 subjects reported a total of 113 (5.9 events per subject) AEs within the first 6 months of treatment with rhIGF-I/rhIGFBP-3 in Clinical study INSM-110-303. Twenty six (79%) of 33 subjects reported a total of 148 (4.5 events per subject) AEs within the first 6 months of treatment with rhIGF-I in Clinical Study 90-111/92-5302-001.

The AEs reported by the most subjects following rhIGF-I/rhIGFBP-3 treatment were injection site erythema (63%), injection site reaction (hair growth, 47%), hypoglycemia (37%), hypertrophy (32 %) and headache (26%). The AEs reported by the most subjects following rhIGF-I treatment were headache (33%), injection site pain (30%), hypoglycemia (21%), pyrexia (18%) and fatigue (12%). The percentage of subjects reporting events and types of events were compatible following rhIGF/rhIGFBP-3 and rhIGF-I treatment.

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<sup>126</sup> In this analysis of study INSM-110-303, the total exposure was 107 subject-months or 5.6 mo/subject ( 16 subjects with 6 months of treatment and 3 subjects who completed an average of 3.7 months). In study 90-111/92-5302-001 the total exposure was 179 subject-months (28 subjects who completed 6 months of treatment and 5 subjects who completed an average of 2.2 months). Subjects in the rhIGF-I were slightly older (11.1 years vs. 8.4 years) and 9 (27%) were pubertal, compared to no pubertal subjects in the rhIGF-I/rhIGFBP-3 study.

The applicant proposes that SAEs were encountered more frequently with rhIGF-I.<sup>127</sup> The following number (and percentage) of patients with SAEs was reported in the rhIGF-I/rhIGFBP-3 group (n= 19): hypoglycemia (1 patient or 5 %), cardiorespiratory failure (1 or 5%), hepatomegaly (1 or 5%), and obstructive bronchitis (1 or 5%). The following number (and percentage) of patients with SAEs was reported for the rhIGF-I group (n =33): hypoglycemia (4 or 12 %), headache (2 or 6%), hypokalemia (2 or 6 %), agitation (1 or 3 %), convulsions (1 or 3 %), dizziness (1 or 3 %), gastroenteritis (1 or 3 %), hypotonia (1 or 3 %), papilledema (1 or 3%), paralysis (1 or 3 %), renal pain 1 or 3 %), sepsis (1 or 3 %), and surgical intervention 1 or 3 %).

## 8.7 Postmarketing Risk Management Plan

The application did not include a postmarketing risk management plan with this application.

## 8.8 Other Relevant Materials

The DDMAC, DSRCS, and DMETS consults have been reviewed and their recommendations have been incorporated in the proposed labeling.

# 9 OVERALL ASSESSMENT

## 9.1 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, mecaseimerin rinfabate has an acceptable benefit-to-risk profile for the proposed indication if used according to the label. Mecasermin rinfabate treatment was effective in increasing linear growth short-term in patients with severe primary IGFD at to-be-marketed doses of 1-2 mg/kg daily. The adverse event profile of mecaseimerin rinfabate, 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 for rhIGF-I; it is also consistent with IGF-I's known mechanisms of action. In general there are no major differences between this reviewer's and applicant's efficacy and safety conclusions.

## 9.2 Recommendation on Regulatory Action

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<sup>127</sup> The applicant proposes that a larger percentage of patients had AEs for hypoglycemia, injection site reaction and headache reported as severe in the rhIGF-I group relative to the rhIGFBP-3 group. Severe adverse events for these AEs (relative to total patients with the respective AE) were as follows: 1) for rhIGF-I: hypoglycemia (4/7 or 57%), injection site reaction (4/10 or 40%), headache (2/11 or 18%); 2) for rhIGF-I/rhIGFBP-3: hypoglycemia (1/7 or 14%), injection site reaction (none), headache (none).

From a clinical perspective, mecasermin rinfabate 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).<sup>128</sup>

### 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

There are unanswered questions concerning the long-term treatment with mecasermin rinfabate, in particular as it relates to the immunogenicity of the product and the theoretical risk of developing neutralizing antibodies (in contrast to endogenous IGFBP-3, rhIGFBP-3 is not glycosylated). Although the data presented to date do not indicate any evidence of neutralizing antibodies, this theoretical risk should be investigated postapproval. The applicant should continue to measure antibodies against rhIGF-I/rhIGFBP-3 and its components and collect long-term efficacy data for height velocity and height SDS with the aim of obtaining final height information.

### 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 revision of the "Clinical Studies" and of the "Adverse Reactions" sections.
- several additions to the "Precautions" section
- a recommendation to add a description of several laboratory and special assessment observations that were observed in the clinical trials
- several changes to the "Indications and Usage" section to harmonize it with the indication already approved for rhIGFI (Increlex).

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<sup>128</sup> In order to harmonize the indication for this product with that of the recently approved recombinant human IGF-I (brand name Increlex), this reviewer recommends to use the term "primary IGF-I deficiency" (primary IGFD) instead of "hereditary growth hormone insensitivity syndrome" (GHIS) proposed by the applicant.

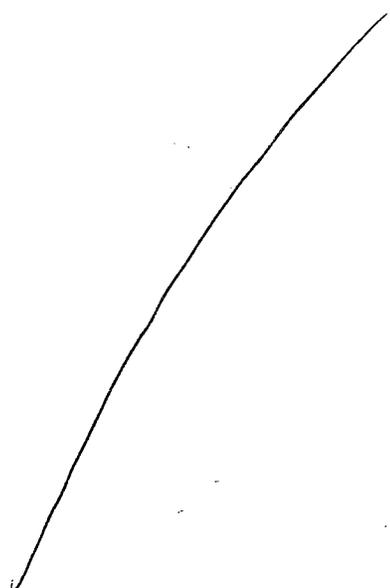
## 9.5 Comments to Applicant

See Phase 4 recommendation.

## 10 APPENDICES

### 10.2 Line-by-Line Labeling Review

#### PROPOSED PACKAGE INSERT



16 Page(s) Withheld

     § 552(b)(4) Trade Secret / Confidential

     § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Clinical Review  
{Dragos Roman}  
{21-884/N000}  
{Mecasermin rinfabate (iPLEX)}

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